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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PAR PHARMACEUTICAL, INC., and PAR STERILE PRODUCTS, LLC, Plaintiffs, v. QUVA PHARMA, INC., STUART HINCHEN, PETER JENKINS, MIKE RUTKOWKSI, DONNA KOHUT, DAVID SHORT, STEPHEN RHOADES, TRAVIS MCGRADY, and DAVID HARTLEY, Defendants.	Civil Action No. 3:17-cv-06115-BRM-DEA **HIGHLY CONFIDENTIAL**

DEFENDANT QUVA'S REPLY BRIEF
IN SUPPORT OF REQUIRED BOND AMOUNT

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Cases

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I. INTRODUCTION

When Par sought its Preliminary Injunction to prohibit the launch of QuVa's ready-to-use (premixed) vasopressin products, it told the Court that it would be irreparably and significantly harmed if those products were to enter the market. In its Response to QuVa's Motion to Set a Bond, Par now pivots 180 degrees. Faced with having to post a sufficient security bond to protect QuVa if it is ultimately determined that QuVa was wrongfully enjoined, Par now claims that QuVa will not be able to launch its products and will not take any substantial market share even if it does. The Court should not countenance Par's about-face. Instead, the Court should require Par to post a bond in the amount requested by QuVa – an amount that is well-supported and consistent with Par's own prior arguments in this case.

II. ARGUMENT

A. Par Misrepresents the Legal Standard and Burden of Proof for Setting a Security Bond

In seeking to prevent QuVa from launching QuVa's premixed vasopressin products, while at the same time avoiding any risk to itself should it later be determined that the preliminary injunction should not have been granted, Par obscures the purposes of the security bond and the policies behind Fed. R. Civ. P. 65(c). Par also misstates the applicable legal standards.

It is well established that one of the main purposes of the bond requirement is to protect against harm to defendants that have been wrongfully enjoined. "The bond

grows out of the idea that because of an attenuated procedure, an interlocutory order has a higher than usual chance of being wrong." *Instant Air Freight Co. v. C.F. Air Freight, Inc.*, 882 F.2d 797, 804 (3d Cir. 1989) (internal citation omitted).

Indeed, "[w]hen setting the amount of security, district courts should ***err on the high side***." *Mead Johnson & Co. v. Abbott Labs.*, 201 F.3d 883, 888 (7th Cir. 2000) (emphasis added); *Arlington Indus., Inc. v. Bridgeport Fittings, Inc.,* No. 3:06-cv-1105, 2011 WL 4916397 at *4 (M.D. Pa., October 17, 2011). Errors in setting the bond too high are of very little consequence because the bond is not automatically paid in full to a defendant if it is determined that the preliminary injunction should not have issued. *Mead Johnson,* 201 F.3d at 888. Rather, the enjoined defendant must establish actual damages after any such determination. *Id.* "Unfortunately, an error in [setting the bond too low] produces irreparable injury, because the damages for an erroneous preliminary injunction cannot exceed the amount of the bond." *Id.*; *see also Instant Air Freight*, 882 F.2d at 804 (stating that "with rare exceptions, a defendant wrongfully enjoined has recourse only against the bond").

Another function of the security bond is to deter "rash applications" for preliminary injunctions. *Instant Air Freight*, 882 F.2d at 804. "Shifting back to the plaintiff the complete injury occasioned by the errors that sometimes occur when preliminary relief is issued after an abridged judicial inquiry will hold in check the

incentive business rivals have to pursue relief that gives them a competitive edge even if…they lose in the end." *Mead Johnson*, 201 F.3d at 888. "The rule limiting liability to the amount of the bond provides the plaintiff with notice of the maximum extent of her liability. The bond can thus be seen as a contract in which the court and plaintiff 'agree' to the bond amount as the 'price' of a wrongful injunction." *Instant Air Freight*, 882 F.2d at 805, n. 9 (citation and quotations omitted). Here, rather than pay full price for its injunction, Par wants a bargain basement discount.

In addition to misrepresenting the nature of bond requirement, Par also improperly elevates the standard of proof for determining the bond amount. Although Par cites cases from the Second Circuit stating that a party need only provide a rational basis for the bond it seeks (Dkt. 178, "Par. Br." at 6), it then repeatedly relies on *Luminara* for the proposition that the "bond calculation must be supported by evidence that is at least as strong as the evidence supporting a damage calculation submitted at trial." (Par Br. at 6, 9, 10.) There are no other reported cases that apply this standard for *setting* a bond amount, and certainly none that are controlling on this Court.[1]

[1] The *Luminara* court itself was not *setting* a bond, rather, it was ruling on a motion to *modify* a bond. *Luminara Worldwide, LLC v. Liown Elecs. Co.*, No. 14-cv-3103, 2015 WL 3559273, at *4 (D. Minn. May 27, 2015). Moreover, the burden of proof was likely influenced by the court's belief that the bond did not limit recoverable damages. *Id.* at *8. This proposition has been squarely rejected by the Third Circuit. *Sprint Commc'ns Co. v. CAT Commc'ns Int'l, Inc.*, 335 F.3d 235, 241 (3d Cir. 2003). And the *Latuszewski* case cited by Par (Par Br. at 7) relates to the

Under the proper standard, "the party enjoined must show that *damage* is certain; not that the *amount* of damage is certain." *Lewis Galoob Toys v. Nintendo of Am., Inc.*, No. 90-cv-1440, 1991 WL 1164068, at *2 (N.D. Cal. Mar. 27, 1991) (emphasis added). In *Galoob*, the court stated that the defendants' burden to establish potential damages for a bond is no greater than that the plaintiff was required to establish in order to show likelihood of success. *Id.* Par's requirement for exacting proof of actual damage in setting the bond is likely to result in unduly limiting the cap on recovery in contravention of the policies behind Fed. R. Civ. P. 65(c), and has no apparent support in the controlling case law in this Circuit.

B. QuVa has Provided Reliable Evidence Sufficient to Support its Requested Bond Amount

1. QuVa's COO's declaration testimony is properly supported by a non-speculative damages calculation.

Par ironically complains that QuVa's evidence is "self-serving" and "speculative." (Par Br. at 8.) But when Defendants questioned Dr. Meyer's evidence of irreparable harm as speculative during the preliminary injunction proceedings, Par argued that courts in this District "recognize that in forecasting future events, there will be some speculation." (Dkt. 96 at 13.) What is good for the goose is good for the gander.

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quantum of evidence needed to *collect* on the bond, not to *set* the bond amount. *Latuszewski v. VALIC Fin. Advisors, Inc.*, 393 F. App'x 962, 966-67 (3d Cir. 2010).

Further, courts have recognized that "[t]he wrongfully enjoined…party's proof of damages 'does not need to be to a mathematical certainty.'" *Nokia Corp. v. InterDigital, Inc.*, 645 F.3d 553, 559 (2d Cir. 2011). Instead, courts regularly accept an enjoined party's reasonable estimates of potential damages, presented either in declarations or otherwise. *Mead Johnson*, 201 F.3d at 887 (holding it was error for district court to reject enjoined party's "soft" estimate); *Arlington Indus.* 2011 WL 4916397, at *5 (M.D. Pa. Oct. 17, 2011) (accepting damages calculation made by enjoined party's CFO on the morning of hearing); *Alexander v. Primerica Holdings, Inc.*, 811 F. Supp. 1025, 1038 (D.N.J. Jan. 7, 1993) (accepting calculation of potential damages presented in enjoined defendant's briefing). QuVa's evidence is more than sufficient in view of the case law.

Par's cases (Par Br. at 6-7) do not compel a different result. In *Luminara*, the court did not reject the defendant's bond proposal because the CEO's declaration was speculative, but because there was no evidence of mitigation. *Luminara,* 2015 WL 3559273, at *6. Whereas in *Fox,* defendants did not take into account the scope of the injunction and did not present evidence of lost profits. *Fox Television Stations, Inc. v. BarryDriller Content Sys.,* 915 F. Supp. 2d 1138, 1149 (C.D. Cal. 2012).

Par's criticism that the marketing assessment supporting QuVa's damages estimate (Dkt. 176-1, Ex. 2, Declaration of Peter Jenkins ("Jenkins Dec.," at Ex. A) is an "unsupported" litigation inspired "summary" falls flat because the marketing

assessment *itself* is the "underlying document" that supports Mr. Jenkins' projections.[2] [redacted] (Supplemental Declaration of Peter Jenkins dated April 12, 2018 ("Supp. Jenkins Dec."), at ¶ 9.) [redacted] (Id.) In any event, there is nothing nefarious about QuVa's obviously necessary preparation of its projected damages in connection with this proceeding; it is based on QuVa's business model and was prepared using QuVa's internal business information.

As for Par's grievance regarding supposedly "withheld" documents, any such documents were not relevant or responsive to Par's expedited discovery requests, as limited by agreement of the parties and Magistrate Judge Arpert. (Dkt. 89-4, Ex. 409 at 14:20-25:7). Further, the expedited discovery phase in this case ended in November 2017, and no further discovery has been ordered by the Court since that time. Par's intimations that "underlying" documents should have been provided to it are thus wrong and directly contrary to this Court's orders on expedited discovery.

[2] Par's cases regarding the inadmissibility of evidence summaries at trial (Par Br. at 9-10) are simply not relevant, as QuVa's market projection submitted with the Jenkins Declaration is not a summary.

Aside from Mr. Jenkins' damages estimate, QuVa's expert Dr. Rao has also concluded that QuVa expects to lose significant profits due to the preliminary injunction. (Dkt. 176-1 at Ex. 1, ¶ 12.) Mr. Jenkins' calculations are further supported by *Par's* expert Dr. Meyer, in her declaration testimony regarding Par's alleged irreparable harm. Specifically, Dr. Meyer repeatedly states that Par will lose significant sales based on QuVa's launch of a competing vasopressin product, and the accompanying loss of revenue will have significant harmful effects on Par. (Dkt. 69-3, ¶¶ 13, 16, 21-26.) It necessarily follows that Par could not be irreparably harmed due to loss of sales to QuVa unless those sales are substantial.

Even Par's current opposition to the bond includes an exhibit that, like *all of the evidence* in this case, [redacted]: "…we estimated a compounded [vasopressin] product had the potential to ultimately take ~30% of market share." (Dkt. 178-5, Ex. 7.)

In the final analysis, QuVa's estimate of damages in the amount of $102 million is well-supported and reasonable in a pharmaceutical case of this nature. There is nothing excessive about this projected loss of product sales by QuVa during the injunction period, particularly given the significant sales and revenues generated for Vasostrict®. And despite its repeated refrain that QuVa's requested bond is egregiously high, Par has never indicated that it is unable to pay.

2. Par's attack on QuVa's premises fails to undermine QuVa's evidence.

According to Par, QuVa's proposed bond amount is wrong due to QuVa's supposedly incorrect assumptions regarding four "critical factors." To the contrary, it is Par that fails to appreciate how these factors affect a proper bond determination.

[redacted]

[redacted]

Par further argues that because its own follow-on vasopressin product did not quickly gain market share despite "a full-time sales force to market the product," QuVa's projections must be wrong. (Par Br. at 18; Dkt. 178-1, Declaration of Antonio Pera ("Pera Dec.") at ¶ 4.) [redacted]

[redacted] This is consistent with Mr. Pera's testimony that PharMEDium's purchase of Vasostrict® vials dropped 50%, even without a competing product in the market. (Pera. Dec. at ¶ 6.)

Finally, Par argues that the legal distinction between restitution and damages somehow makes its own prior arguments regarding irreparable harm irrelevant to the question of the bond amount. (Par Br. at 21.) No doubt Par wishes to hide from its prior statements, which now support QuVa's position that QuVa's products would capture a significant part of the market. *See Davis v. Wakelee*, 156 U.S. 680, 689 (1895) (stating "[w]here a party assumes a certain position in a legal proceeding, and succeeds in maintaining that position, he may not thereafter, simply because his interests have changed, assume a contrary position"). Specifically, not only did Par argue that QuVa's vasopressin product would directly compete with Vasostrict® and injure Par (Dkt. 96 at 13), Par's expert Dr. Meyer also predicted a parade of horribles that would result from "substantial sales" lost due to launch of QuVa's products. These harms purportedly included harm to Endo's stock price and loss of ability to

raise capital and make capital expenditures and R&D investments. (Dkt. 69-3 at ¶¶ 13, 16, 21-26.) None of this could come to pass if the effect of QuVa's product on the market would be zero to minimal, as Par now claims.

In his Declaration submitted with QuVa's opening brief (Dkt. 176-1 at Ex. 1 "Rao Dec."), Dr. Rao opined that Dr. Meyer's opinions regarding irreparable harm were consistent with his own calculation of QuVa's potential lost profits due to the preliminary injunction. (Rao Dec. at ¶ 12.) Tellingly, Par failed to challenge this opinion.

The trial date. Par's speculation that the court will set a trial date in this case just nine months from now is unwarranted and in any event, irrelevant. The procedural posture of this case alone shows the fallacy of Par's predicted trial date. Par has recently significantly expanded the case by filing its first amended complaint (Dkt. 114, "FAC"), adding five new defendants and new allegations. The FAC is subject to several motions to dismiss that have not been resolved. (Dkts. 167, 168, 182, 183.) It makes no sense to commence discovery when it is unclear which parties and claims will remain in suit.

Even if Par is correct that trial will be completed sooner than QuVa predicts, the amount of the bond should be set using QuVa's later date because the amount of the bond circumscribes QuVa's maximum recovery. In other words, any damages collectable by QuVa must be based on the time it is enjoined. If that amount of time

is less than eighteen months, then QuVa cannot collect on eighteen months of lost profits. On the other hand, if the bond is set based on an earlier trial date and the time QuVa is enjoined exceeds that time, QuVa has no recourse. In fact, in setting an appropriate bond, many courts calculate damages through appeal, which this Court could properly choose to do as well in setting the bond. *See Alexander*, 811 F. Supp. at 1038.

The FDA Guidance. Finally, Par speculates that the FDA will remove vasopressin from the "Category 1" list, and then discounts the amount of the bond based on only a 10% probability that QuVa would be able to market its vasopressin products given this potential regulatory action. This discount is legally improper in the context of setting a bond. *Arlington Indus.*, 2011 WL 4916397 at * 5 (reconsidering prior discounted bond amount, stating "it is manifestly unjust to put the risk of loss of 75% of its damages on the party enjoined"). If vasopressin is later removed from the "Category 1" list, this can be taken into account when QuVa moves to collect on the bond.

Even if Par is correct that the FDA will remove vasopressin from the "Category 1" list, this will not occur until the end of 2018 at the earliest. (Dkt. 178-5 at Ex. 13, ¶ 7.) [redacted] In any event, the risks associated with potential future regulatory action should not be borne by QuVa

in setting the *ceiling* on its damages. *See Galoob Toys*, 1991 WL 1164068 at *3 (holding risk of potential market shifts should not be borne by enjoined defendant in setting the bond amount).

C. Par's Counterproposals Should be Rejected

Par accuses QuVa of failing to support its requested security bond. Yet, Par's three counterproposals – no security bond at all, $10,000, or $1,000,000 – are legally improper and lack any connection whatsoever to QuVa's potential damages. *Am. Standard, Inc. v. Lyons Indus., Inc.*, No. 97-cv-4806, 1998 WL 35256926, *14 (D.N.J. Feb. 17, 1998) (finding inadequate Plaintiff's proposal for the amount of bond because there was no "evidence to indicate [the amount] is … appropriate … to cover such costs and damages as may be incurred or suffered by [the enjoined defendant]") (internal quotation omitted).

First, no bond at all is almost *never* appropriate, and is especially inappropriate where, as here, damages to QuVa are all but certain. "The law in [the Third] Circuit is clear – when a risk of financial harm exists for the party to be enjoined, the posting of a security bond is required." *Alexander*, 811 F. Supp. at 1036; *see also, Frank's GMC Truck Ctr., Inc. v. Gen. Motors Corp.*, 847 F.2d 100, 103 (3d Cir. 1988) ("While there are exceptions, the instances in which a bond may not be required are so rare that the requirement is almost mandatory").

Par's remaining low-ball proposals should also be rejected. *Alexander*, 811 F. Supp. at 1038 ("Where a defendant wrongfully enjoined would suffer significant economic harm, posting of a nominal bond would defeat the very purposes of the bond requirement…and is not supported by the case law in this circuit"); *Galoob Toys*, 1991 WL 1164068 at *4 ("[The bond amount] should not restrict the enjoined party from proving after trial the full extent of its forecast damages"). *Neo Gen*, cited by Par, only supports the application of a nominal bond where there is *no* evidence of harm to the enjoined party. *Neo Gen Screening, Inc. v. TeleChem Int'l, Inc.*, 69 F. Appx. 550, 556 (3d Cir. 2003). Plainly, *Neo Gen* is inapposite and a nominal bond is not proper in this case.

If Par truly believes that there is no longer any imminent threat of irreparable harm to it, and does not wish to post a fair bond, the Court should revisit its prior holding that a preliminary injunction is warranted in this case. *See Sprint*, 335 F.3d at 240 (holding that upon grant of injunction, the "[plaintiff] then decides whether to accept the preliminary relief by posting the bond or to withdraw its request").

III. CONCLUSION

For the foregoing reasons, and the reasons set forth in QuVa Pharma Inc.'s Opening Memorandum of Law in Support of its Requested Bond, QuVa respectfully requests that the Court order Par to post a bond in the amount of $102 million within 10 business days of the ruling on this motion.

Dated: April 13, 2018

s/ Stephen M. Orlofsky

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Attorneys for Defendants

CERTIFICATE OF SERVICE

I certify that on this date, I caused a copy of the foregoing Defendant QuVa's Reply Brief in Support of Required Bond Amount to be served upon all counsel of record via the Court's ECF system.

Dated: April 13, 2018

s/ Stephen M. Orlofsky

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IN THE UNITED STATES DISTRICT COURT
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PAR PHARMACEUTICAL, INC., and PAR STERILE PRODUCTS, LLC, Plaintiffs, v. QUVA PHARMA, INC., STUART HINCHEN, PETER JENKINS, MIKE RUTKOWKSI, DONNA KOHUT, DAVID SHORT, STEPHEN RHOADES, TRAVIS MCGRADY, and DAVID HARTLEY, Defendants.	Civil Action No. 3:17-cv-06115-BRM-DEA **HIGHLY CONFIDENTIAL**

SUPPLEMENTAL DECLARATION OF PETER JENKINS IN SUPPORT OF QUVA'S MOTION TO SET REQUIRED BOND AMOUNT

I, Peter Jenkins, declare as follows:

1. I make this supplemental declaration in support of Defendant QuVa Pharma Inc.'s Motion to Set Required Bond Amount.

2. In connection with preparation of this supplemental declaration, have reviewed the following documents, which I understand have been redacted to remove Plaintiffs' Highly Confidential information:

- Plaintiff Par Pharmaceutical Inc. and Par Sterile Products, LLC's Response to Defendant's Motion to Set Required Bond Amount, including Exhibits 1-16;
- Declaration of Dr. Christine S. Meyer in support of Plaintiffs' Response to Defendant's Motion to Set Required Bond Amount;
- Declaration of Antonio Pera in support of Plaintiffs' Response to Defendant's Motion to Set Required Bond Amount; and
- Declaration of Michael J. Miller in support of Plaintiffs' Response to Defendant's Motion to Set Required Bond Amount.

3. Dr. Miller's assertion that QuVa will not be prepared to market its premixed vasopressin products in the U.S. until November 2018, is incorrect. [redacted]

[redacted]

[redacted]

4. Attached to this supplemental declaration as Exhibit A is an internal QuVa report [redacted]

[redacted]

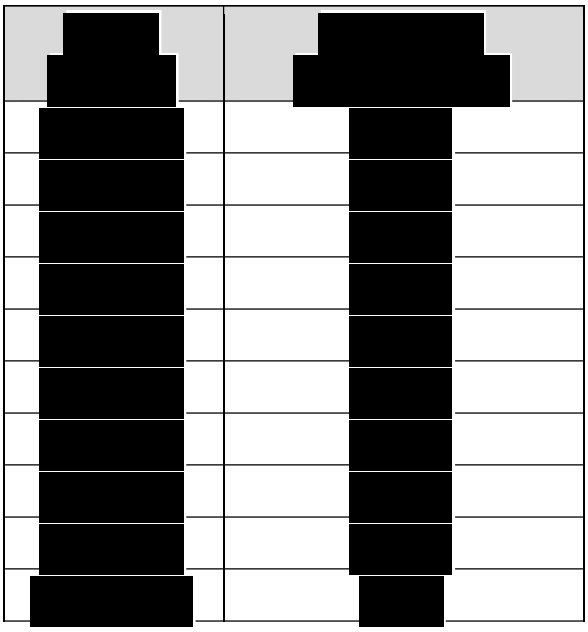
5. Dr. Miller is incorrect that amino acid testing and related compounds (impurity) testing is required prior to marketing of QuVa's premixed vasopressin products. (Miller Decl. at ¶¶ 10-12.) [redacted]

6. [redacted]

7. [redacted]

8. [redacted]

[redacted]



9. Plaintiffs assert that QuVa has not produced any internal QuVa documents to substantiate its projected market share of its pre-mixed vasopressin products. This assertion is simply incorrect. [redacted]

[redacted] Over the course of our careers in the pharmaceutical industry, and specifically during our time at Mayne Pharma and JHP Pharmaceuticals, Stuart Hinchen and I have prepared at least 30-40 market assessments using the same approach in connection with planning for launch of a generic product into an existing generic market or a generic product into a proprietary (monopoly) market.

10. Evaluation of expected market share after a generic compounded product launch includes [redacted] Mr. Hinchen and I have significant experience in this regard.

11. [redacted]

12. I disagree with Mr. Pera that QuVa will be prevented from penetrating the market due to potential delays in obtaining approval from hospitals to supply our premixed vasopressin products. (Pera Decl. at ¶ 3.) I am not currently aware of any obstacles that would delay hospital approval of those products. In my experience, hospitals move quickly when they are motivated to do so, where, as here, [redacted]

13. [redacted]

[redacted]

14. I also disagree with Dr. Meyer's assertion that QuVa will not likely capture PharMEDium's sales of its compounded vasopressin product. (Meyer Decl. at ¶ 16.) As noted by Dr. Meyer, PharMEDium has been ordered by the California State Board of Pharmacy to cease and desist compounding drug products for shipment into California because those drug products "pose an immediate threat to the public health or safety." (*Id.*; Ex. 1 to Lustberg Declaration.) I disagree with Dr. Meyer that PharMEDium's "regulatory limitations" "affect only the California market." (Meyer Decl. at ¶ 16.) Dr. Meyer has understated the extent of PharMEDium's production challenges and the ripple effect of the California action.

15. In December 2017, PharMEDium suspended operations at their largest manufacturing facility after inspections by the U.S. Food and Drug Administration ("FDA"). (Exhibit B, February 9, 2018, Memphis Daily News Article.) In January 2018, the FDA issued a report of inspection detailing, *inter alia*, repeated observations of PharMEDium personnel's failure to follow procedures designed to prevent microbiological contamination of drug products purporting to be sterile. (Exhibit C, January 5, 2018, FDA Report of Inspection.) As of February 2018, PharMEDium's parent company, AmerisourceBergen Corp. has acknowledged receiving a grand jury subpoena from prosecutors in the U.S. attorney's office for the Western District of Tennessee related to its drug production facility in Memphis. (Exhibit B, February 9, 2018, Memphis Daily News Article.) And it has been reported that "investors are concerned about how the company will get the Memphis plant back up and running." (*Id*.)

16. In view of PharMEDium's well-publicized failures to comply with FDA and state safe manufacturing practices and the entry of the California cease and desist order, [redacted]

17. As noted in paragraphs 6 and 11 of my March 23, 2018, declaration, aside from PharMEDium's extensive production problems, [redacted]

[redacted]

18. [redacted]

19. [redacted]

[redacted] This is further support for why QuVa expects strong demand for its premixed vasopressin products.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Date: April 12, 2018

Peter Jenkins

Exhibit A
FILED UNDER SEAL

Exhibit B

Supplemental Declaration Of Peter Jenkins In Support Of QuVa's Motion To Set Required Bond Amount

Pa.-based Drug Company Subpoenaed Over Memphis Plant

By Andy Meek

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Pennsylvania-based drug wholesaler AmerisourceBergen Corp. has acknowledged receiving a grand jury subpoena from prosecutors in the U.S. Attorney's Office for the Western District of Tennessee related to its drug production facility in Memphis.

In a security filing, the company said its subsidiary, PharMEDium, had received the subpoena "seeking various documents, including information generally related to the laboratory testing procedures of PharMEDium's products, and more specifically, for PharMEDium products packaged in a certain type of syringe" at the Memphis facility, which has been closed since December and remains closed.

The company said it is in discussions with prosecutors and has started producing documents related to the subpoena. AmerisourceBergen CFO Tim Guttman told analysts during the company's first quarter earnings call in recent days that the company's facility here is its largest.

"They're roughly, ballpark, maybe half of our production capacity," Guttman said. "They're highly automated. They're some robotics and some automation equipment there. So, they're not only large, but they're very efficient."

He said the company anticipates reopening in Memphis during the current quarter.

The company suspended operations in Memphis in December after inspections by the U.S. Food and Drug Administration, and said the closure will lower its core profit in 2018 by some $60 million.

The company posted a first quarter profit of $861.9 million on Tuesday, Feb. 6, and raised its adjusted earnings per share estimate for the year to a range of $6.45 to $6.65, up from $5.90 to $6.15. However, a Deutsche Bank analyst told Reuters that investors are concerned about how the company will get the Memphis plant back up and running.

Morningstar 16:00 EST

Real Time Updates

Symbol	Chg	Chg%	Last
Morningstar	18.65	0.28%	6,567.11
Small Cap	10.35	0.11%	9,473.22
Nasdaq			

TDN Video — News, Training & Events

- Journalist Roundtable
- MLGW CEO J.T. Young
- Judge Larry Potter on Environmental Court

RECORD TOTALS	DAY	WEEK	YEAR
PROPERTY SALES	106	106	5,260
MORTGAGES	115	115	6,250
FORECLOSURE NOTICES	0	0	966
BUILDING PERMITS	137	137	10,874
BANKRUPTCIES	71	71	3,845
BUSINESS LICENSES	32	32	2,053
UTILITY CONNECTIONS	61	61	2,277
MARRIAGE LICENSES	19	19	1,049

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Exhibit C

Supplemental Declaration Of Peter Jenkins In Support Of QuVa's Motion To Set Required Bond Amount

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
404 BNA Dr., Bldg. 200, Ste 500 Nashville, TN 37217-2597 Phone: (615) 366-7801 Fax: (615) 366-7802 Industry Information: www.fda.gov/oc/industry	11/27/2017-01/05/2018
	FEI NUMBER 3004153061

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Brenda L. Womack, General Manager

FIRM NAME	STREET ADDRESS
PharMEDium Services, LLC.	913 N. Davis Ave.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Cleveland, MS 38732-2106	Outsourcing Facility

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION #1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed.

****THIS IS A REPEAT OBSERVATION FROM THE 2013 & 2015 INSPECTIONS****

Specifically,

1) On 11/27/2017 and 11/28/2017, we observed the firm's technicians preforming aseptic processing for sterile drug products and the following significant aseptic technique deficiencies were observed, which were also deviations from the firm's SOP CPS-313, titled "ASEPTIC TECHNIQUE AND CLASSIFIED AREA MANAGEMENT", Version 4 Effective Date: 02/28/17:

a) We observed compromise of the ISO 5 work areas by technicians leaning and over-reaching into the hoods to retrieve material that had been placed behind the product being filled on several occasions. This action placed the technician's arm in front of the laminar air flow allowing for turbulence to occur above the product.

b) We observed technicians not sanitizing hands/wrist with sterile (b) (4) prior to entering/re-entering ISO 5 work areas on numerous occasions.

c) We observed technicians to have continuous rapid movements in the ISO 5 hood work areas during aseptic processing especially while observing for particulate matter after filling plastic IV bags.

2) A review of the firm's security surveillance video, ((b) (4)) regarding 3 mcg/mL Fentanyl Citrate and 0.05% Bupivacaine HCL in Sodium Chloride 0.9% Lot #172760060C dated 10/04/2017 that failed endotoxin

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FOOD AND DRUG ADMINISTRATION

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testing, noted the following significant aseptic technique deviations, which were also deviations from the firm's SOP CPS-313, entitled "ASEPTIC TECHNIQUE AND CLASSIFIED AREA MANAGEMENT" Version 4 Effective Date: 02/28/17:

a) The technician did not sanitize their gloves upon re-entering the ISO 5 hood work area at least 41 times during processing of this lot.

b) The technician was observed leaning and over-reaching into the ISO 5 hood work area at least 19 times during processing of this lot.

c) The technician was observed touching items in the trash container on 3 occasions and then re-entering the ISO 5 hood work area without sanitizing/changing their gloves during processing of this lot.

d) The return airflow to the ISO 5 hood was observed to be blocked by the technician and equipment at least 6 times during processing of this lot.

e) The technician used the (b) (4) in the ISO 5 hood work area without sanitizing the unit at least 4 times during processing of this lot.

f) The technician placed an electronic weigh scale into the ISO 5 hood work area without sanitizing the unit during processing of this lot.

OBSERVATION #2

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

Your firm has been experiencing potency (over and under) failures with combo drug families such as; Fentanyl/ Bupivacaine and Fentanyl/Ropivacaine from the 2 mcg/mL to 7 mcg/mL concentration. Also, your firm has been

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experiencing potency failures with non-combo drug families such as; Hydromorphone with the concentrations of 0.04 mg/mL to 2 mg/mL and Morphine with the concentrations of 1mg/mL to 10mg/mL. Per the firm's CAPA #055 dated 07/13/2017, the firm has had a total of 152 Total Confirmed Potency Failures from 01/16/2017 to 10/26/2017.

The (b) (4) deliver the quantity of each active drug ingredient and the diluent for the (b) (4) per specification for each drug product. As of 11/07/2017, the (b) (4) are no longer utilized for drug product lots that require active drug ingredients of (b) (4). Drug lots that require (b) (4) (b) (4) are currently (b) (4) by (b) (4). This change was based on an analysis of failure results where a majority of the failures were (b) (4) of the active drug ingredient delivered by the (b) (4) The equipment manual for the (b) (4) declares "Acceptable volume ranges between (b) (4)."

Your firm has been using (b) (4) since 2013 for the (b) (4), which contain active drug ingredients and the diluent.

A review of numerous opened and closed Nonconformance Reports (NCR), noted that it appears that your (b) (4) are not capable of consistently delivering the proper amount of active drug ingredients or diluent to ensure that finished drug products are within acceptable specifications. Therefore, your firm is relying solely on finished drug product testing to release drug products for distribution. The NCRs reviewed noted the following:

a) NCR #CNC-17-322 dated 10/03/2017 regarding the over potency testing results for Lot #172750002C and Lot #172750004C.

Per this investigation, based on the potency result of 0.225 mg/ml for Lot #172750002C, the (b) (4) of hydromorphone HCL 10 mg/ml delivered to the (b) (4) (b) (4) was (b) (4). This was (b) (4) (b) (4) than the recipe amount (b) (4) The (b) (4) of diluent delivered was (b) (4) (b) (4) which amounted to an under-delivery of (b) (4).

Per this investigation, based on the potency result of 0.214 mg/ml for Lot #172750004C, the (b) (4) of hydromorphone HCL 10 mg/ml delivered to the (b) (4) was (b) (4). This was (b) (4)

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(b) (4) than the recipe amount (b) (4) The (b) (4) of diluent delivered was (b) (4) which amounted to an under-delivery of (b) (4)

b) NCR #CNC-17-324 dated 10/04/2017 regarding the over potency testing results for Lot #172760009C.

Per this investigation, based on the potency result of 0.211 mg/ml for Lot #172760009C, the (b) (4) of hydromorphone HCL 10 mg/ml delivered to the (b) (4) was (b) (4). This was (b) (4) (b) (4) than the recipe amount (b) (4) The (b) (4) of diluent delivered was (b) (4) which amounted to an under-delivery of (b) (4).

c) NCR #CNC-17-327 dated 10/05/2017 regarding the over potency testing results for Lot #172770003C.

Per this investigation, based on the potency result of 0.215 mg/ml for Lot #172770003C, the (b) (4) of hydromorphone HCL 10 mg/ml delivered to the (b) (4) was (b) (4). This was (b) (4) (b) (4) than the recipe amount (b) (4) The (b) (4) of diluent delivered was (b) (4) which amounted to an under-delivery of (b) (4).

d) NCR #CNC-17-383 dated 10/10/2017 regarding the under-potency testing results for Lot #172830001C.

Per this investigation, the under-delivery of drug solution, coupled with the over-delivery of diluent could possibly explain the out-of-limit (OOL). A procedural change to CPS-606 has been submitted and approved for implementation on 11/05/2017 to (b) (4) CAPA-055 will be closed, and a new CAPA (corporate-wide) will continue to monitor the effectiveness of this change by noting any effect on the number and rate of potency OOL's. It should be noted that the above NCRs for over/under potency drug products used the firm's (b) (4) for delivery of (b) (4) of the active drug ingredients to (b) (4).

OBSERVATION #3

Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

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****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

During a walk-through of your facility on 11/27/17 and 11/28/17, we observed the following objectionable conditions during compounding operations in your ISO 5 and 7 environments:

a) Rusted metal hinges on plastic totes used to store in-process and finished drug products in your ISO 7 cleanroom

b) White film residue on wall surfaces of three of your ISO 5 hoods

c) Chipped paint on floor surface of your ISO 7 cleanroom

d) Gray paint residue on walls in your ISO 7 cleanroom

e) Foreign material residue on rubber wheels, located on your metal carts used to transport materials through-out your ISO 7 cleanroom

OBSERVATION #4

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

Environmental monitoring for non-viable particulates is not performed at sufficient frequencies to represent routine production conditions within the ISO 5 and ISO 7 areas of your cleanroom. According to CPS-707, Microbiological and Environmental Testing, Version 23, Effective Date: 10/06/17, your firm performs non-viable monitoring in the ISO 5 areas on a (b) (4) basis. You stated your ISO 7 cleanroom area also follows this same monitoring schedule.

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OBSERVATION #5

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

a) Your firm had the ISO 7 compounding room (cleanroom) floor resurfaced on two occasions, from 09/01/2017 to 09/04/2017 and from 09/14/2017 to 09/17/2017 by an outside contractor. Prior to this resurfacing on both occasions, all (b) (4) of the ISO 5 LAFHs and other processing equipment were covered with plastic and moved to an unclassified area for storage during this timeframe. After completion of resurfacing on both occasions, the ISO 5 hoods were moved back into the ISO 7 compounding room. Sterile drug processing began in these hoods on 09/05/2017 after the first resurfacing and on 09/17/2017 after the second resurfacing. The ISO 5 hoods were not recertified until 09/22/2017 and the ISO 7 compounding room was not recertified until 09/23/2017. Your firm failed to recertify the ISO 7 cleanroom and ISO 5 LAFHs prior to processing sterile drug products to ensure that the hoods and compounding room were operating within acceptable specification.

b) The certification of your ISO 5 Laminar Airflow Hoods, which is performed and documented every (b) (4), indicates repairs for HEPA Filter Leaks in the following Hoods:

- Hood (b) (4) (b) (4) 2017 documented HEPA Filter Leaks)
- Hood (b) (4) (b) (4) 2017 documented HEPA Filter Leaks)
- Hood (b) (4) (b) (4) 2017 documented HEPA Filter Leaks)
- Hood (b) (4) September 2017 documented HEPA Filter Leak)
- Hood # (b) (4) ((b) (4) 2017 documented HEPA Filter Leaks)
- Hood # (b) (4) ((b) (4) 2017 documented HEPA Filter Leaks)
- Hood # (b) (4) (September 2017 documented HEPA Filter Leak)
- Hood # (b) (4) (March 2017 documented HEPA Filter Leak)
- Hood # (b) (4) (September 2017 documented HEPA Filter Leak)
- Hood # (b) (4) ((b) (4) 2017 documented HEPA Filter Leaks)

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• Hood # (b)(4) ((b) (4) 2017 documented HEPA Filter Leaks)

Hood #'s (b) (4) had documented HEPA Filter Leaks during both the (b) (4) and (b) (4) 2017 certifications. Your firm failed to take corrective actions regarding sterile drug products processed, inside the above listed ISO 5 Hoods, between documented repairs for HEPA Filter Leaks.

OBSERVATION #6

Samples taken of drug products for determination of conformance to written specifications are not representative.

Specifically,

A review of processing records noted concerns with your firm's current sampling methods for sterile injectable finished drug products. For example, your firm is only pulling (b) (4) for sterility/endotoxin (sample pulled needs to be (b) (4) for testing) and (b) (4) for potency/ID (sample pulled needs to be (b) (4) for testing) testing. Per management, the largest finished batch size processed at this facility is approximately (b) (4) (b) (4) units of finished sterile drug product. These samples are pulled only on a (b) (4) basis which is not representative of the entire batch manufacturing process (beginning, middle, and end).

Also, the largest (b) (4) batch size is approximately (b) (4) (b) (4) of finished drug product. The firm does not sample (b) (4) for potency. Per the firm's CAPA #055 dated 07/13/2017, the firm has been having quantity delivery concerns with the (b) (4) delivering the required amount of active drug ingredients and diluent, which has a direct impact on potency.

OBSERVATION #7

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

****THIS IS A REPEAT OBSERVATION FROM THE 2015 INSPECTION****

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Specifically,

1. Your firm conducted an efficacy study to support a (b) (4) time for (b) (4). Your 2017 microbial/environmental logs document, on numerous occasions, spore-forming bacteria in your ISO 5 and ISO 7 zones despite cleaning efforts. Although a disinfectant effectiveness study appears to have demonstrated that a (b) (4) (b) (4) time was sufficient for the sporicide, the supplier recommends a (b) (4) time.

2. Sterile cleaning solutions are compounded and assembled (if not ready to use) in an unclassified area and then transferred into the ISO 7 and ISO 5 environments for use.

3. Your firm uses unfiltered, non-sterile (b) (4) in the preparation of an (b) (4) solution, which is used in the sanitization process as a sporicidal agent for the cleaning of injection sites (vial stoppers and IV ports) prior to aseptic processing. This solution is also prepared in an unclassified area prior to being utilized in the ISO 5 classified area.

4. According to your firm's SOP CPS-310, entitled "SANITATION OF VIAL STOPPERS AND BAG INJECTION PORTS INCLUDING PREPARATION OF SANITIZATION SOLUTION" Version 5, Effective Date: 05/22/17, (b) (4) However, your firm has not conducted any studies supporting the (b) (4) documented in your SOP.

OBSERVATION #8

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

****THIS IS A REPEAT OBSERVATION FROM THE 2015 INSPECTION****

Specifically,

Your firm has had several media fill failures, which indicate that your aseptic techniques are not properly performed. During 2016 and 2017, your firm had a total of 9 media fill failures. Your firm's investigations do not

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properly address the products that were processed by the technicians that failed the media fills.

For example: Per CNC-17-075 dated 02/20/2017, the technician ((b) (6)) had two media fill failures on 02/15/~~201.~~ 2017 nos. The failed test results, regarding the two media fills, were not obtained until 02/20/2017. The investigation concluded that the video footage provided substantial evidence that the processing technician ((b) (6)) had multiple procedural violations relating to improper sanitizations during aseptic processing per CPS-313. Your firm did not perform any type of corrective actions/investigations as to the sterile drug products that were produced by the technician ((b) (6)) on the 02/15/2017, 02/16/2017, 02/17/2017, and 02/20/2017, which included Lot #'s 170450032C, 170460041C, 170460048C, 170460026C, 170480001C, 170470015C, 170470038C, 170500024C, 170500032C, and 170500034C. These Lots were released for distribution.

OBSERVATION #9

The production area air supply lacks an appropriate air filtration system.

****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

A review of the firm's dynamic smoke study videos, dated March 2017 of the ISO 7 cleanroom environment certification, indicated that the pressure differential (airflow) between the cleanroom and ante rooms appeared neutral. According to the smoke study report, signed by QA on 04/03/17, "(b) (6) recommends that an (b) (4) (b) (4) (b) (4) ."

OBSERVATION #10

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

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****THIS IS A REPEAT OBSERVATION FROM THE 2015 INSPECTION****

Specifically,

a) Your firm uses a (b) (4) to remove particulate matter during the (b) (4) process of all finished sterile drug products except Ephedrine drug products. Your firm has not validated the use of these (b) (4) to determine the compatibility of the (b) (4) with the products nor is the (b) (4) use/lot number documented in the batch record.

b) Your firm uses a (b) (4) in the processing of sterile Ephedrine drug products ((b) (4) different item codes) during the (b) (4) process. Your firm has not validated the use of this (b) (4) to determine the compatibility of the (b) (4) with the product nor is the (b) (4) use/lot number documented in the batch record. Also, the firm does not perform a (b) (4) after use of this (b) (4)

c) Your firm has not validated the process for manufacturing sterile finished drug products contained in 250 mL (b) (4) Bags ((b) (4) product codes), 250 mL Blue Cassettes ((b) (4) product codes), 250 mL Yellow Cassettes ((b) (4) product codes), and 250 mL White cassettes ((b) (4) product codes).

d) Your firm does not perform daily checks on scales ((b) (4) total scales) prior to use. These scales are (b) (4) (b) (4) depending upon usage. The scales are used for weighing (b) (4) (b) (4) of active ingredient, (b) (4) (b) (4) containing diluent and active ingredient, and finished product containers. Per management, these scales are calibrated in house every (b) (4).

OBSERVATION #11

Containers and closures are not tested for conformance with all appropriate written procedures.

****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

Your firm does not conduct any sampling/testing upon receipt of sterile finished injectable drug ingredients,

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CITY, STATE AND ZIP CODE Cleveland, MS 38732-2106	TYPE OF ESTABLISHMENT INSPECTED Outsourcing Facility

product containers or closures; they are approved/released by Quality Assurance without testing. Since raw materials are not tested upon receipt to your facility, potentially defective products are released by your quality unit and utilized in compounding operations. On 11/28/17, your firm initiated a supplier corrective action request (SCAR) for missing graduations on syringes used to produce lot 173310013C HYDROmorphone HCl 1mg/mL on 11/28/17. Since initiation of the SCAR, your firm continued to use this lot of syringes to compound eight (8) additional lots of finished product (173340014C, 173340016C, 173340017C, 173340018C, 173340019C, 173340020C, 173340021C, 173340022C). All products listed have been released by your QA department without resolution of this investigation.

OBSERVATION #12

Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

On 11/27/17 during a walk-through of your facility, we observed the storage of two (2) clear in-process containers filled with 10 mcg/ml Fentanyl Citrate in Sodium Chloride 0.9% Lot# 173300032C contained in plastic IV bags, which was awaiting labeling in the staging area. Additionally, we observed one (1) opaque container of Morphine Sulfate 1mg/mL Lot# 173250006C located in the finished product vault. The lid to the storage container was left ajar, allowing light to contact the product. According to labeling on both raw ingredients and compounded products, both are light sensitive and specify to "protect from light." Your SOP, CPS-013, "Storage and Handling of Inventory" Version 13, Effective Date: 06/29/17 also states, "(b) (4) ."

OBSERVATION #13

Batch production and control records do not include complete labeling control records, including specimens or copies of all labeling used for each batch of drug product produced.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Marvin D. Jones	Marvin D. Jones, Investigator Saundrea A. Munroe, Investigator	01/05/2018

MDJ 1/5/18

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
404 BNA Dr., Bldg. 200, Ste 500 Nashville, TN 37217-2597 Phone: (615) 366-7801 Fax: (615) 366-7802 Industry Information: www.fda.gov/oc/industry	11/27/2017-01/05/2018
	FEI NUMBER 3004153061

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Brenda L. Womack, General Manager

FIRM NAME	STREET ADDRESS
PharMEDium Services, LLC.	913 N. Davis Ave.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Cleveland, MS 38732-2106	Outsourcing Facility

Specifically,

A review of several batch records revealed that these records do not contain samples of the original approved primary, secondary, and case labels applied to the finished drug product.

OBSERVATION #14

Procedures describing the handling of all written and oral complaints regarding a drug product are not followed.

Specifically,

On 09/11/17, your firm performed a recall (RE-17-017) that originated from a consumer complaint regarding illegible expiration date on product label. Per your SOP CPS-007, Recall Procedure, Version 8 Effective Date: 05/04/17, you "will remove the product from the field and then notify the appropriate FDA District office." Your firm did not notify the FDA until inquiry during this inspection.

Additionally, there were 6 recalls performed in 2015 in which zero (0) of them were reported to the FDA. Three (3) (HHE-15-017, HHE-15-020, HH-15-023) were potency related due to stability failures. HHE-015-002 was initiated due to broken syringe caps, HHE-15-022 was initiated due to a cut off expiry date, and HHE-015-026 was initiated due to syringe discoloration. All recalls listed, except for identified stability failures, originated from consumer complaints.

OBSERVATION #15

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

****THIS IS A REPEAT OBSERVATION FROM THE 2013 INSPECTION****

Specifically,

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Marvin D. Jones	Marvin D. Jones, Investigator Saundrea A. Munroe, Investigator	01/05/2018

MDJ 1/5/18

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Brenda L. Womack, General Manager

FIRM NAME	STREET ADDRESS
PharMEDium Services, LLC.	913 N. Davis Ave.
CITY, STATE AND ZIP CODE Cleveland, MS 38732-2106	TYPE OF ESTABLISHMENT INSPECTED Outsourcing Facility

a) All but 20 of the drug products manufactured by your firm contain preservatives. Your firm does not perform preservative testing on finished sterile injectable drug products that contain preservatives to ensure the concentration is within acceptable specification.

b) Your firm does not test the pH for finished sterile injectable drug products.

c) Your firm does not perform negative controls during the microbial testing of environmental monitoring samples.

OBSERVATION #16

The labels of your outsourcing facility's drug products do not include information required by section 503B(a)(10)(A).

Specifically,

The following information is not found on your drug product labels:

a) The date that the drug was compounded.
b) A list of active and inactive ingredients, identified by established name and the quantity or proportion of each ingredient.

Examples of drug product labels that do not contain this information include:

- Morphine Sulfate 1 mg per mL in 0.9% Sodium Chloride Injection (55 mL in 60 mL BD syringe)
- Morphine Sulfate 1 mg per mL Injection (2 mL in BD syringe)
- Fentanyl Citrate 2 mcg per mL and Bupivacaine HCl 0.125% in Sodium Chloride 0.9% Injection (100 mL, 250 mL)
- Morphine Sulfate 5 mg per mL in 0.9% Sodium Chloride Injection (30 mL in 35 mL Monoject Barrel, 50 mL Cassette Reservoir)

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MPJ
1/5/18

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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CITY, STATE AND ZIP CODE Cleveland, MS 38732-2106	TYPE OF ESTABLISHMENT INSPECTED Outsourcing Facility

- Fentanyl Citrate 20 mcg per mL in Sodium Chloride 0.9% (100 mL)
- Fentanyl Citrate 2 mcg per mL and Ropivacaine HCl 0.2% in Sodium Chloride 0.9% Injection (100 mL)
- Fentanyl Citrate 10 mcg per mL in Sodium Chloride 0.9% (250 mL)
- HYDROmorphone HCl 1 mg/mL in Sodium Chloride 0.9% (30 mL)
- Lidocaine HCl 2% 20 mg per mL (10 mL)
- Midazolam HCl 2 mg per mL in Sodium Chloride 0.9% (50 mL)
- Rocuronium Bromide 10 mg per mL Injection (5 mL)
- Ropivacaine HCl 0.2% in Sodium Chloride 0.9% (100 mL yellow cassette reservoir)

~~OBSERVATION #17~~ Observation Deleted. MDJ 1/5/2018

~~Your outsourcing facility has not submitted a report to FDA identifying a product compounded during the December 1, 2016, through May 31, 2017, reporting period as required by section 503B(b)(2)(A).~~

~~Specifically,~~

~~The following combination drug products were compounded and not identified on your June 2017 report:~~

- ~~Sufentanil Citrate and Bupivacaine HCl in 0.9% Sodium Chloride~~
- ~~Sufentanil Citrate and Ropivacaine HCl in 0.9% Sodium Chloride~~
- ~~Fentanyl Citrate and Bupivacaine HCl in 0.9% Sodium Chloride~~
- ~~Fentanyl Citrate and Ropivacaine HCl in 0.9% Sodium Chloride~~
- ~~Hydromorphone HCl and Bupivacaine HCl in 0.9% Sodium Chloride~~
- ~~Hydromorphone HCl and Ropivacaine HCl in 0.9% Sodium Chloride~~ MDJ 1/5/2018

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Marvin D. Jones	Marvin D. Jones, Investigator Saundrea A. Munroe, Investigator	01/05/2018

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PAR PHARMACEUTICAL, INC., and PAR STERILE PRODUCTS, LLC, Plaintiffs, v. QUVA PHARMA, INC., STUART HINCHEN, PETER JENKINS, MIKE RUTKOWKSI, DONNA KOHUT, DAVID SHORT, STEPHEN RHOADES, TRAVIS MCGRADY, and DAVID HARTLEY, Defendants.	Civil Action No. 3:17-cv-06115-BRM-DEA **HIGHLY CONFIDENTIAL**

DECLARATION OF HAROLD PATTERSON IN SUPPORT OF QUVA'S MOTION TO SET REQUIRED BOND AMOUNT

I, Harold Patterson, declare and state as follows:

1. I am the same Harold Patterson who has submitted previous declarations in the matter. I am submitting this declaration in Response to the Declaration of Dr. Michael J. Miller in Support of Plaintiffs' Response to Defendants' Motion to Set Required Bond Amount ("Miller Bond Declaration").

2. I have reviewed the Miller Bond Declaration. I have also reviewed the April 12, 2018 Supplemental Declaration of Peter Jenkins in Support of QuVa's Motion to Set Required Bond Amount ("Supplemental Jenkins Declaration"), including Exhibit A to that Supplemental Declaration.

3. In the Miller Bond Declaration, Dr. Miller states that in his opinion, [redacted]. Dr. Miller makes this claim based upon his belief that [redacted] (Miller Bond Decl. at ¶¶ 5-30.) Dr. Miller also states that [redacted] (Miller Bond Decl. at ¶ 3.) [redacted] (*Id*.) I disagree with Dr. Miller.

4. QuVa is preparing to produce premixed vasopressin products that are in a "ready to use" ("RTU") formulation. QuVa is producing these products under the exemptions to the Food, Drug and Cosmetic Act (FD&C Act) provided to them under sections 503A and 503B of the Act. One of the exemptions is to section 505 of the Act, which describes the approval of new drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs). If QuVa were producing their product as a generic drug pursuant to section 505 of the FD&C Act, then QuVa would be subject to the requirements for an ANDA drug approval and would need to demonstrate equivalency to the Par NDA product by testing their product with an equivalent set of specifications. Since QuVa is planning to produce its RTU vasopressin products under the exemptions granted to them as a 503B outsourcing facility, this is not required. Instead, QuVa is required to manufacture a product that meets specifications that QuVa sets for that product and is in accordance with the applicable cGMP regulations (*Guidance for Industry – Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* ("Guidance"), attached as Exhibit A.) Dr. Miller's opinions fail to account for this difference.

5. Section G of the Guidance states that 21 CFR sections 211.165 and 211.167 apply to the testing and release requirements for compounded products

such as QuVa's vasopressin products. The Guidance also states that the specification for a given compounded product must address the attributes of the product necessary to ensure the quality of the finished drug product and must include at a minimum:

a. Identity and strength of the active ingredient

b. For drug products purported to be sterile, a limit for visible particles

c. For drug products purported to be sterile and/or non-pyrogenic, sterility and a limit for bacterial endotoxins.

(Exhibit A at 14-16.)

6. The USP monograph for Vasopressin Injection, attached as Exhibit B, describes a similar set of specifications and requirements. The product is required to:

a. Possess an activity of not less than 90.0 percent and not more than 110.0 percent of the label claim expressed as USP Vasopressin units;

b. Contain no more than 17.0 Endotoxin Units per USP Vasopressin Unit;

c. Have a pH between 2.5 and 4.5;

d. Meet the requirements for particulate matter in injections <788> under small-volume injections (as a compounded, ready to administer product, QuVa's product would be tested under the requirements in <788> for large-volume); and

e. Meet the requirements under the USP for Injections and Implanted Drug Products <1>.

(Exhibit B.)

7. [redacted]

8. Dr. Miller's analysis of QuVa's readiness to manufacture and test its RTU vasopressin products is based on the status of QuVa's RTU vasopressin products as of November 2017 and [redacted]

9. [redacted]

[redacted]

10. [redacted]

11. [redacted]

12. [redacted]

13. [redacted]

14. Dr. Miller also mentions the need for compatibility testing in his Bond Declaration. (Miller Bond Decl. at ¶¶ 28-30.) [redacted]

15. In my opinion, Dr. Miller fails to account for the fact that even for NDA products, specific process validation parameters (other than aseptic process validations) are quite often performed post-approval of the product (extensions of pre-sterile hold times, extensions of shelf life testing) and that the products produced during these periods of process validation are still saleable products as long as the individual lot produced meets all of the process parameters specified in the process validation protocol. [redacted]

[redacted]

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Date: April 12, 2018

Harold Patterson

Exhibit A

Declaration of Harold Patterson In Support Of QuVa's Motion To Set Required Bond Amount

Guidance for Industry

Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Brian Hasselbalch (CDER) at 301-796-3279.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2014
Current Good Manufacturing Practices (CGMPs)

Guidance for Industry

Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
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druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2014
Current Good Manufacturing Practices (CGMPs)

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry[1]

Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This interim guidance describes FDA's expectations regarding compliance with current good manufacturing practice (CGMP) requirements for facilities that compound human drugs and register with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated if it is not produced in accordance with CGMP. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211.[2] FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. Until final regulations are promulgated, this guidance describes FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 during this interim period. This guidance is only applicable to drugs compounded in accordance with section 503B.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) and in cooperation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] Positron emission tomography (PET) drug products are subject to CGMP regulations at 21 CFR part 212 and are not covered by this guidance.

II. BACKGROUND

The Drug Quality and Security Act adds a new section 503B to the FD&C Act.[3] Under section 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products compounded in a registered outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FD&C Act[4] and the requirement to label drug products with adequate directions for use under section 502(f)(1) of the FD&C Act[5] if the requirements in section 503B are met.[6] Outsourcing facilities will be inspected by FDA and must comply with other provisions of the FD&C Act, including CGMP requirements under section 501(a)(2)(B).

Under section 501(a)(2)(B), a drug is deemed to be adulterated if

> the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess . . . .

Further, section 501 of the FD&C Act, as amended by the Food and Drug Administration Safety and Innovation Act,[7] states

> for the purposes of paragraph (a)(2)(B) the term 'current good manufacturing practice' includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

Generally, CGMP requirements for finished drug products are established in 21 CFR parts 210 and 211.

FDA intends to develop specific CGMP regulations applicable to outsourcing facilities. Until those new regulations are promulgated, this guidance describes FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 during this interim period.

This interim guidance reflects FDA's intent to recognize the differences between compounding outsourcing facilities and conventional drug manufacturers, and to tailor CGMP requirements to the nature of the specific compounding operations conducted by outsourcing facilities while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products.

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[3] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

[4] 21 U.S.C. 355.

[5] 21 U.S.C. 352(f)(1).

[6] Drug products produced in accordance with section 503B are also exempt from the track and trace requirements in section 582 of the FD&C Act.

[7] Pub. L. No. 112-114, 126 Stat. 993 (2012).

FDA intends to focus its inspectional and enforcement efforts on those aspects of outsourcing facility compounding operations that pose the highest risk to patient safety. In particular, the primary focus of this guidance is on those aspects of 21 CFR part 211 that relate to sterility assurance of sterile drug products and the safety of compounded drug products more generally, with respect to strength (e.g., subpotency, superpotency), and labeling or drug product mix-ups.

III. CGMP FOR OUTSOURCING FACILITIES

A. Facility Design

21 CFR part 211, "Current Good Manufacturing Practice for Finished Pharmaceuticals," sets out the requirements applicable to the design of facilities used in the manufacture, processing, packing, or holding of a drug product (§ 211.42).[8] Certain elements of facility design are considered critical to ensuring the quality of compounded sterile drug products. For example, all processing and controlled areas must be clean and free of visible signs of filth, dirt, mold or mildew, insects, and inappropriate items or debris (see also, § 211.56). In addition, the following elements should be met by outsourcing facilities:

- Damaged, dirty, or discolored HEPA filters should not be used.
- Sterile drugs should be produced only in ISO 5 or better air quality (see Table 1).

Table 1 describes cleanroom classification standards as established in ISO 14644-1 Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness.

Table 1. ISO Classification of Particulate Matter in Room Air*

Class Name		Particle Count	
ISO Class	**U.S. FS 209E**	**ISO, m^3**	**FS 209E, ft^3**
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3,520	100
6	Class 1,000	35,200	1,000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

*Limits are in particles of 0.5 µm and larger per cubic meter [current ISO] and cubic feet measured under dynamic conditions. Adapted from former Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 14644-1:1999, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3,520 particles of 0.5 µm per m^3 or larger (ISO Class 5) is equivalent to 100 particles per ft^3 (Class 100) (1 m^3 = 35.2 ft^3).

- The facility should be designed and operated with cascading air quality (e.g., by proper air classification and air pressurization) to protect the ISO 5 zone (or critical area[9]). The

[8] In this section, unless otherwise indicated, all references to "§" or "section" refer to Title 21 of the Code of Federal Regulations.

[9] A *critical area* is an area designed to maintain sterility of sterile materials. See FDA guidance for industry, *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

facility layout, room separation, and process flow should be designed in a manner to prevent the influx of contamination from adjacent areas and rooms of lower air quality, and to avoid any disruption of HEPA unidirectional flow.

- The air cleanliness classification of the area surrounding the ISO 5 zone immediately adjacent to the aseptic processing line should meet, at a minimum, ISO 7 (Class 10,000) standards.
- If an isolator is used, the surrounding area should meet at least ISO 8 (Class 100,000) standards.

The ISO 5 zone or critical area must be qualified (i.e., shown to meet the specifications; see §§ 211.42 and 211.113(b)). Qualification should include at least the following studies and tests, which should be documented as having been conducted, including the particular conditions under which the studies and tests were conducted.

- Airflow studies should be conducted under dynamic conditions (e.g., in-situ smoke study) to initially qualify the HVAC/HEPA unit *and* when any changes are made to the HVAC/HEPA unit or the critical area that might affect airflow. Any indication of poor air control (e.g., non-laminar, turbulent) should be corrected before use.
- HEPA periodic testing/recertification should be performed at least twice a year to ensure that appropriate air flow and quality is maintained. These tests should include integrity testing of the HEPA filters, particle counts, and air velocity checks.
- Velocities of unidirectional air should be measured six inches from the HEPA filter face and at a defined distance close to the work surface in the ISO 5 area.
- If any portable ISO 5 units are moved from one location to another, re-qualification should be performed before resuming sterile compounding in the unit.

The clean areas in which components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred should be designed to minimize the level of particle contaminants in the final product. The microbiological content (bioburden) of articles and components that are subsequently sterilized should be controlled.

B. Control Systems and Procedures for Maintaining Suitable Facilities

To prevent contamination or mix-ups during the course of sterile and other operations, § 211.42 requires separate or defined areas or other similar control systems for a facility's operations.[10] Section 211.56 requires that procedures be established and followed that assign responsibility for sanitation and describe in detail the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities. In addition to the requirements in §§ 211.42 and 211.56, the following control systems and procedures are considered critical to ensuring the quality of compounded sterile drug products and should be implemented at outsourcing facilities:

[10] For example, this would be necessary when using powders because of how the powder particles can drift in the air. However, such separation may not be needed if working with a non-sterile liquid (at that processing step).

- Large equipment present in the cleanroom should not obstruct air vents and/or air flow to compromise aseptic operations.

- Pressure differentials, humidity, and temperatures

Pressure differential limits should be established, and control systems should include built-in alarms to detect excursions. Monitoring for pressure differentials, humidity, and temperatures should occur during production, and prompt action should be taken to correct inappropriate conditions. If a problem cannot be immediately corrected, production should stop until corrected.

Monitoring procedures should require documentation and investigation of any instances in which there is a loss of positive pressure in the clean room during actual production, the lots affected, and the corrective action taken. System alarms may not be necessary if differentials are regularly checked during operations (checks should be scheduled considering the environment, such as use of an isolator versus a less protected process) and the results recorded in logs and evaluated against pre-specified alert and action limits at each check.

- Powder drugs

If powder drugs are handled, procedures should be established and followed to appropriately manage cross-contamination risk, particularly if the powder is cytotoxic or highly sensitizing. FDA recommends the physical segregation of areas in which powder drugs are exposed to the environment. For penicillin/beta-lactam products, a separate facility (or physically separate space) is required (see § 211.42(d)).

- Multiple manipulations, multi-use facilities

Processes and procedures should minimize contamination risks posed by, for example, the number and complexity of manipulations, number of simultaneous operations and workstations, and the staging of materials used in the process.

For multi-use facilities and non-dedicated equipment, changeover and cleaning procedures should be established and followed to prevent cross-contamination between products.

- Cleaning and disinfection of clean areas and equipment sterilization

Procedures for cleanroom cleaning and disinfecting should be established. Procedures for cleaning and disinfecting ISO 5 areas/units should include instructions for consistently and properly cleaning and disinfecting surfaces that are difficult to access. Sterile disinfectants and lint-free sterile wipes should be used for disinfecting all critical areas. Procedures should describe the methods and schedule for cleaning and include the use of sporicidal disinfectants in the ISO 5 area and classified rooms on a regular basis.

The suitability, efficacy, and limitations of the disinfecting agents being used should be monitored. The expiration dates of disinfection solutions should be closely monitored. Published literature and supplier certificates can be relied on when initially determining the

effectiveness of agents used to clean and disinfect the facility and equipment surfaces provided that the supplier's cleaning procedures are followed.

Critical equipment surfaces that come in contact with sterile drug products, containers, and closures should be sterile; disinfection alone is not sufficient (see section D below).

Based on the results of environmental monitoring (see section C below), the sanitation program and other practices should be revised if there are indications that the frequency of disinfectant use or the type of disinfectant being used is inadequate to ensure appropriately clean surfaces.

C. Environmental and Personnel Monitoring

21 CFR 211.42(c)(10)(iv) requires establishing a system for monitoring environmental conditions in aseptic processing areas, while §§ 211.113(b) and 211.28(a) require personnel sanitation practices and gowning to be both acceptable and qualified for the operations they perform. Procedures for monitoring the environment and personnel for the presence of viable particles[11] and non-viable particles should be established and followed as described here.

Environmental monitoring should consist of a well-defined program that evaluates the potential routes of microbial contamination of the human drug that could arise from the air, surfaces, process, operation, and personnel practices. The program should contain an appropriate detection component to verify state of control of the environment. In particular, the program should achieve the following:

- Cover all production shifts and include monitoring during normal production conditions
- Include at least daily monitoring of the ISO 5 zone during operations
- Establish alert and action limits and appropriate responses to each
- Describe use of sampling (e.g., contact plates, swabs, active air samplers), alert and action limits, and testing methods (e.g., media, plate exposure times, incubation times and temperatures) that are designed to detect environmental contaminants, including changes in microflora type and amount
- Be supported by an evaluation of the choice of the sampling locations and sampling methods

Personnel monitoring should consist of a well-defined program that does the following:

- Includes a routine program for daily/shift monitoring of operators' gloves and an appropriate schedule for monitoring gowns during operations
- Establishes limits that are based on the criticality of the operation relative to the contamination risk to the product

[11] A *viable particle* is a particle that consists of, or supports, one or more live microorganisms (see ISO 14644-6:2007; Cleanrooms and Associated Controlled Environments-Part 6: Vocabulary).

- Calls for an investigation of results that exceed the established levels or demonstrate an adverse trend, a determination of the impact on the sterility assurance of finished products intended to be sterile, and the development and execution of appropriate corrective actions

Procedures should include establishing the validity of the microbiological media, including the preparation, sterilization, and growth potential of the media used in performing tests, including environmental and personnel monitoring.

D. Equipment, Containers, and Closures

Several provisions of part 211 address controls over the equipment used to compound and containers and closures in which the compounded drug product is packaged (§§ 211.65, 211.67, 211.80, 211.82, 211.84, 211.87, 211.94, 211.113). A number of equipment and container/closure controls are considered critical to ensuring the quality of compounded drug products and are expected to be implemented by outsourcing facilities.

Equipment, containers, and closures that come into contact with the drug product must be evaluated to ensure adequacy for intended use, including for holding or storing sterilized equipment, containers, or closures to ensure sterility and cleanliness at time of use (see §§ 211.80, 211.84(d)(6), 211.65, 211.67(a)).

If the outsourcing facility does not use pre-sterilized and depyrogenated single-use equipment (e.g., filters, transfer tubing, temporary storage containers) and containers and closures (e.g., vials, syringes), the equipment, containers, and closures must be sterilized and depyrogenated before first use through sterilization and depyrogenation processes that have been validated, that is, demonstrated and documented to consistently achieve the desired result when performed under defined conditions (see §§ 211.67(a), (b) and 211.94(c)).

Each lot of equipment, containers, and closures must be examined to verify identity and tested to ensure conformity with appropriate specifications before use (see §§ 211.84(d) and 211.67(b)). The Agency does not intend to take action against an outsourcing facility regarding the identification or testing of each lot of single-use equipment, containers, and closures if (1) for a finished drug product intended to be sterile, the supplier certifies and labels the material as ready-to-use, sterile, non-pyrogenic; (2) the supplier's packaging integrity is verified upon receipt before use; and (3) the certificate of analysis (COA) provided by the supplier is reviewed to verify that the product is represented to meet the required specifications established by the outsourcing facility, including sterility and depyrogenation. Any single-use equipment, container, or closure not meeting acceptance requirements must be rejected or not used until rendered suitable for use (see §§ 211.84(d), (e) and 211.67(a)).

The following additional controls are critical:

- Equipment

Equipment must be qualified as capable of performing its intended functions or operations before first use, and procedures for routine calibration and maintenance established and followed (see § 211.68). Equipment surfaces that come in contact with components, in-process materials, or drugs must not be reactive, additive, or absorptive so as to alter the quality of the drug (see § 211.65).

- Containers and closures

Scientifically sound and appropriate criteria for containers and closures must be established to ensure that drug product containers and closures used for compounded drug products are suitable for each particular drug product for which they will be used (see § 211.160(b)). Appropriate procedures must be established for testing the containers and closures at the time they are selected to determine whether they meet the criteria for use; the tests and results must be documented (see §§ 211.84(d)(3), 211.184). As part of the selection process, integrity testing of the drug product container closure system should be performed to verify its ability to maintain the quality of the finished drug product and sterility over the expiry period. Integrity testing should be performed again if the supplier or specifications of the container/closure is changed.

Procedures for storage if appropriate, of sterilized containers or closures must be established in a manner to minimize the risk of contamination and to maintain sterility (see § 211.80(a), (b)). After storage for long periods or after exposure to air, heat, or other conditions that might adversely affect the drug product container, or closure, containers and closures must be re-tested or re-examined for identity, strength, quality, and purity (see § 211.87). However, the Agency does not intend to take action against an outsourcing facility regarding this additional testing if each lot of containers or closures is stored under the supplier's labeled storage conditions and protected from contamination when portions of the lot are removed.

E. Components

Controls over the source and quality of components are required, particularly when using non-sterile materials, or ingredients when producing compounded drug products, especially sterile drug products (§§ 211.82, 211.84, 211.87, 211.113). The following controls are considered critical to ensuring the quality of compounded drug products and are expected to be implemented by outsourcing facilities.

Appropriate specifications must be established for the components used in each drug product (see § 211.160(b)). Specifications should address the attributes necessary to ensure the quality of the finished drug product. Attributes can include: identity, strength, purity, particle size, sterility, bacterial endotoxin level, or other characteristics that could affect the quality of the final drug product.

Each lot of components must be tested to verify identity and evaluated for conformity with appropriate specifications before use (see § 211.84). The Agency does not intend to take action

against an outsourcing facility regarding the identification or testing of each lot if all of the following conditions are met:

- The component is an approved finished human drug product.
- The component was purchased directly from a manufacturer who has registered and listed with FDA under section 510 of the FD&C Act without repacking or other alteration since initial manufacture, or was purchased from a distributor that certifies that the component has not been subject to repacking or other alteration since initial manufacture.
- The label of each lot of the component has been examined to verify that the component meets required specifications before use.
- The shipment's package integrity has been verified upon receipt before use.

Any component not meeting acceptance requirements must be rejected (see § 211.84(e)).

Components (e.g., bulk active ingredients and excipients, but not an approved finished drug product), must be tested to verify identity and evaluated for conformity with appropriate specifications, and, if necessary, depending on intended use, endotoxin level and sterility before use in compounding (see § 211.84). As described in § 211.84(d)(2), in lieu of testing each shipment of each ingredient, a COA can be accepted from the supplier and evaluated to determine whether the lot can be used, provided that the following conditions are met:

- The reliability of the supplier's analyses has been established at appropriate intervals (i.e., no less frequently than annually for active ingredients and every two years for other components) through appropriate steps to confirm the supplier's test results for those tests relevant to the specifications established for the compounded drug product, and to confirm that the ingredient meets the applicable USP or NF monograph, if one exists.[12]
- At least one identity test has been conducted to confirm that the component is the one specified in the purchase order.

In addition, as required by § 211.82(a):

- Each container or grouping of containers of components must be examined to verify appropriate labeling regarding contents.
- The shipment's package integrity must be verified upon receipt before use.

Acceptance of incoming lots of nonsterile components (including water) must include microbial and endotoxin testing (see § 211.84(d)(6)). The Agency does not intend to take action against an outsourcing facility regarding this testing if the water is purchased and certified as sterile and non-pyrogenic, and is accompanied by a COA. The quality of water produced on-site and used as

[12] Components (bulk drug substances and other ingredients) used in compounding must comply with the standards of the applicable US Pharmacopeia or National Formulary monograph, if such monograph exists (see sections 503B(a)(2)(B) and (a)(3) of the FD&C Act).

a component or processing aid should be tested regularly at point of use to verify acceptable microbial quality and endotoxin limits.

Components must be re-tested or re-examined for identity, strength, quality, and purity after storage for long periods or after exposure to air, heat, or other conditions that might adversely affect the component (see § 211.87). However, additional testing is unnecessary if each lot of components is stored under the supplier's labeled storage conditions, used within the supplier's labeled re-test or expiration date, and protected from contamination when portions of the lot are removed.

Alternative Approach for Comment
Reducing the Need for Laboratory Testing of Incoming Components

FDA is requesting public comment on possible alternative approaches that would enable an outsourcing facility to have confidence in the quality of incoming components without periodic laboratory testing following initial qualification testing to confirm the information in the supplier's certificate of analysis (COA). For example, FDA is considering the following possible alternative approach that could reduce the need for duplicative testing by multiple outsourcing facilities. Comments are requested on this or any other possible alternative approaches.

Under this potential alternative approach, FDA would not intend to take action against an outsourcing facility regarding additional testing to confirm the supplier's COA if (1) the supplier submits to FDA a drug master file (DMF) containing the information outlined below, (2) FDA has reviewed the DMF and issued a letter to the DMF holder stating that FDA has no further comments, (3) the DMF holder has provided a copy of that letter to the outsourcing facility, and (4) the outsourcing facility maintains a copy of the letter that can be produced during an inspection. To avoid devoting resources to reviews of DMFs that would never be relied upon, FDA would only review the DMF upon receipt of a letter from an outsourcing facility indicating its intent to rely on the DMF to fulfill its component testing requirements.

If the supplier is the original manufacturer of the component, the supplier's DMF would need to contain the following current information:

- A description of the testing performed before release and shipment of a component lot to the outsourcing facility and the specific quantitative (or qualitative, if applicable) results of a representative lot
- A description of packaging, labeling, tamper-evident seals, and other features used to ensure package integrity while in distribution
- Examples of testing records, such as chromatographs and spectrographs
- A commitment to update the DMF if any testing performed is significantly modified
- A commitment to notify outsourcing facilities under specified circumstances, including but not limited to, a change in specifications or identification of a problem with the quality of a component already shipped to the outsourcing facility

If the supplier is not the original manufacturer of the component (e.g., the supplier is a repackager), the supplier DMF would need to contain the following current information:

- A description of the testing performed before release and shipment of a component lot to the outsourcing facility and the specific quantitative (or qualitative, if applicable) results of a representative lot
- A description of quality assurance activities performed, including:
  - how the supplier ensures that the original manufacturer of the component has not changed
  - how new sources (i.e., other than the original manufacturer) of components are qualified
  - a commitment to convey the identity of the manufacturer of each lot (i.e., within the COA) to the outsourcing facility
  - a commitment to state in each COA that the ingredient was transported through a supply chain fully known to the supplier
  - how often a source is requalified to ensure acceptable quality on an ongoing basis
- A description of packaging, labeling, tamper-evident seals, and other features used to ensure package integrity while in distribution
- Examples of testing records, such as chromatographs and spectrographs
- A commitment to update the DMF if the procedures described above are significantly modified
- A commitment to notify component purchasers under specified circumstances, including but not limited to, a change in specifications or identification of a problem with the quality of a component already shipped to the outsourcing facility

F. Production and Process Controls

Production and process controls are required when producing any drug product (see e.g., §§ 211.22, 211.25, 211.28, 211.100, 211.111, 211.113, 211.188, 211.192). The following controls are considered critical to ensuring the quality of compounded sterile drug products and are expected to be implemented by outsourcing facilities.

1. General Production and Process Controls

Written procedures for production and process control must be established and followed to ensure the consistent production of a drug that meets the applicable standards of identity, strength, quality, and purity (see § 211.100). These procedures should ensure documentation that all key process parameters are controlled and that any deviations from the procedures are justified.

Batch records must provide complete documentation of production of each batch of drug product (see § 211.188). The actual batch output (yield) should be compared to the projected (calculated) output for each drug product. If the actual output is different than expected after accounting for sampling and known process loss, this finding should be considered an indicator of a potential problem with production and should be investigated. An acceptance level for actual output

should be established that ensures lot-to-lot consistency. Failure to meet the acceptance criterion must be investigated before approving lot release and may require that the lot be rejected (see § 211.192).

If a drug product intended to be sterile is not terminally sterilized, it is critical that in-process controls include sterile filtration (see § 211.113(b)), preferably just before filling into the final product container.

Storing or holding materials during processing (e.g., prior to sterilization; post-sterilization prior to container fill), also called *hold times*, must be assessed (see §§ 211.110(c), 211.111). Hold time(s) for production phases for a drug product should be limited. Limits should be supported by data and based on an understanding of the associated risk of increased bioburden and increased level of endotoxin. Hold time assessments can be performed as part of the process for validating sterility assurance.

2. Aseptic Drug Processing

Introductory training on aseptic technique, cleanroom behavior, gowning, and procedures covering aseptic manufacturing area operations must be established and conducted before an individual is permitted to enter the aseptic manufacturing area or conduct operations in a laminar flow hood (see § 211.25(a)). Once introductory training outside of the aseptic manufacturing area is completed, further training based on department-specific requirements and individual job descriptions should be conducted. An individual would be considered qualified to conduct aseptic operations after having passed at least three successful, successive media fill simulations designed to verify the adequacy of their technique and behavior. Simulations of production should be conducted in the same area where production occurs.

Techniques intended to maintain sterility of sterile items and surfaces should include the following:

- Sterile materials should be handled only with sterile instruments.
- After initial gowning, sterile gloves should be regularly sanitized during production or, when needed, changed.
- Sterile and non-particle shedding gowning components should be used. Gowning components should be stored such that their sterility is not compromised.
- If an element of a gown is found to be torn or defective, it should be changed immediately.
- Sterile products, containers, closures, or critical surfaces should not directly touch any part of the gown or gloves.
- Personnel should move slowly and deliberately within the cleanroom or hood.
- Personnel should keep their entire body and objects out of the path of unidirectional airflow above containers and products being filled.

Procedures for aseptic processing should address the following considerations:

- The design of equipment used in aseptic processing should limit the number and complexity of aseptic manipulations, and be suitable for its intended use.
- Personnel, material, and process flow should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures, or the surrounding environment.
- In-process material, including intermediates such as stock solutions, should be placed in container-closures that protect the material from the cleanroom environment. Container-closures holding sterile in-process material should not be breached in an environment less than ISO 5.
- Products should be transferred under appropriate cleanroom conditions. For example, transfer, loading, and unloading of aseptically filled product to and from the lyophilizer should occur only in classified areas that provide ISO 5 protection to the partially sealed containers.
- All aseptic manipulations, including processing of sterile materials, filling, and closing (e.g., placement and sealing of stoppers on vials) should be performed under unidirectional air flow that is ISO 5 or better.
- Appropriate steps to prepare equipment for sterilization should be established, such as cleaning and use of wrapping that ensures protection while still allowing penetration of the sterilizing agent.

The validation of sterilization operations (e.g., holding vessels, filling equipment, lyophilizer) and periodic verification activities and results must be documented (see § 211.113(b)). Specifically:

- For sterile drug products that are terminally sterilized, validation should demonstrate that the sterilization process achieved at least a 10^{-6} sterility assurance level (SAL) using an appropriate biological indicator.
- For aseptic processing of sterile drug products (i.e., not subjected to terminal sterilization), validation should be demonstrated by conducting media fills simulating the actual production process.
- For aseptic processing (e.g., filling) of sterile powders, validation should be demonstrated by conducting media fills simulating the actual production process.
- For sterile drug products that are filter sterilized, prefiltration bioburden and endotoxin limits should be established and measured prior to sterile filtration. A pharmaceutical sterilizing-grade filter should be used, and filter integrity testing should be conducted after each filtration or production run.
- For sterile drug products that are not subjected to overkill terminal sterilization, pre-filtration bioburden limits should be established and measured prior to filtration.

Media fill studies should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations. The media fill program should address applicable issues such as the following:

- Factors associated with the longest permitted run of the aseptic processing operation that can pose contamination risk (e.g., operator fatigue, quality of processing environment)
- Representative number, type, and complexity of normal interventions that occur with each run, as well as nonroutine interventions and events (e.g., maintenance, stoppages, equipment adjustments)
- Lyophilization, when applicable
- Aseptic assembly of equipment (e.g., at start-up, during processing)
- Number of personnel and their activities
- Representative number of aseptic additions (e.g., charging containers and closures as well as sterile ingredients) or transfers
- Shift changes, breaks, and gown changes (when applicable)
- Type of aseptic equipment disconnections/connections
- Aseptic sample collections
- Operational configurations in the ISO 5 zone, and line speeds (when applicable)
- Weight checks
- Container closure systems (e.g., sizes, type, compatibility with equipment)
- Specific provisions in written procedures relating to aseptic processing (e.g., conditions beyond which discarding of exposed materials in the ISO 5 area or line clearance is mandated)

G. Release Testing

Sections 211.165 and 211.167 require that finished drug products be tested to determine whether they meet final product specifications before their release for distribution. Section 211.22 establishes that the quality control unit is responsible for ensuring that the finished drug product is not released until this testing is conducted and the results confirm that the finished drug product meets specifications. Procedures for final release testing should be established and followed as outlined here.

Appropriate specifications must be established for each drug product (see § 211.160(b)). Specifications must address those attributes necessary to ensure the quality of the finished drug product (see § 211.160(b)) and should include at a minimum:

- Identity and strength of the active ingredient
- For drug products purporting to be sterile, a limit for visible particles

- For drug products purporting to be sterile and/or non-pyrogenic, sterility and a limit for bacterial endotoxins

Procedures for release must be established that ensure that each batch of a drug product is not released until the following have been completed (see §§ 211.22, 211.165, 211.167(a)):

- Except as described below, an appropriate laboratory determination has been conducted to ensure that each batch of a drug product conforms to specifications.
- Associated laboratory data and documentation have been reviewed by the quality control unit and demonstrate that the drug product meets specifications.
- A designated qualified individual from the quality control unit has authorized final release.

The Agency does not intend to take action against an outsourcing facility regarding the release testing requirements described above, under the following conditions:

- For testing to confirm identity, if specifications have been established and met for strength (potency).
- For sterility testing, if the drug product is terminally sterilized and a validated sterilization cycle that uses bioindicators is employed.
- For sterility testing, if it is *initiated before* batch release (see also Subsection I "Stability/Expiration Dating," below, for information on how to label products released without a completed sterility test) and
  - procedures have been established that specify that if the drug product fails to meet a criterion for sterility, all facilities that received the drug product will be immediately notified of the test results and provided with any appropriate information and recommendations to aid in the treatment of patients;
  - the notification will be documented; and
  - FDA will be notified in writing.[13]
- For sterility testing, if the batch consists of fewer than 10 dosage units[14] compounded pursuant to a prescription for a single patient, and the unit(s) is labeled with a beyond use date (BUD), where the BUD provides reasonable assurance of chemical and physical stability based on literature or other scientific information, and is established according to the following:
  - not to exceed 24 hours at USP controlled room temperature;
  - not more than 3 days refrigerated;
  - not more than 45 days in a solid frozen state between -25° and -10°.

[13] Reports should be submitted to FDA electronically to OFAlertReport@fda.hhs.gov.
[14] One dosage unit is the amount of drug in a labeled dose, e.g., one tablet or one syringe.

If the batch size is very small and does not meet the criteria above for eliminating the sterility test when compounding pursuant to a prescription for a single patient, standard sterility tests may require that additional units be produced to be able to conduct the sterility test. For example, USP <71> "Sterility Tests" is the principal source used for sterility testing methods, and requires that the number of samples for batches of parenteral drug products containing less than 100 containers be 10% or 4 containers, whichever is greater. However, the Agency does not intend to take action against an outsourcing facility regarding the number of units tested if 10% of the containers in the batch is less than 4, and the sterility test is conducted using a number of containers that equals 10% rounded up to the next whole number.

With regard to testing other than sterility testing, for batches of less than 10 units, since complete release testing would require use of a significant proportion of the batch, the Agency does not intend to take action against an outsourcing facility regarding testing on every batch to demonstrate conformity with other specifications such as identity, strength, and particulate, if such testing is performed on samples from every other batch, or once at least 10 units of that drug product have been produced. For example, if the batch size is consistently 5 units, testing should be conducted on every second batch. As another example, if the first batch is 5 units, the second batch is 3 units, and the third batch is 3 units, testing should be performed on the third batch because the minimum of 10 units has been met.

For aqueous solutions, testing for identity and strength can be performed on the bulk solution just before filling the finished drug product containers.

H. Laboratory Controls

When testing components, in-process materials, and finished drug products, laboratory controls must be used to ensure the reliability of the tests (§ 211.160). Each laboratory, whether in-house or external[15] to the outsourcing facility, used to conduct testing of components, in-process materials, or finished drug products must employ the following critical aspects of laboratory controls to ensure the quality of sterile drug products compounded by the outsourcing facility (see §§ 211.160, 211.194):

- Follow appropriate written procedures for the conduct of each test and document the results
- Have sampling and testing procedures designed to ensure that components, in-process materials, and drug products conform to the specifications set for the drug product
- Use analytical methods and equipment that are suitable for their intended use and are capable of producing valid results; if using a validated or an established compendial test procedure in a specification, the test has been verified and documented to work under the conditions of actual use

[15]When an outsourcing facility seeks the services of a contract facility to perform all or part of the testing of a drug, the outsourcing facility's quality control unit is responsible for approving and rejecting drugs tested by the contractor . See 21 CFR 200.10(b); 21 CFR 211.22(a); and FDA draft guidance for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM353925.pdf.

- Keep complete records of all tests performed to ensure compliance with established specifications and standards, including examinations and assays

Alternative Approach for Comment
Minimize Need for Facilities to Have an In-House Laboratory

FDA is requesting public comment on a possible alternative approach that would minimize the need for outsourcing facilities to establish an in-house laboratory to perform final release testing, while providing confidence about the accuracy of testing performed by a third-party. For example, FDA is considering the following possible alternative approach. Please comment on this or any other alternatives.

A laboratory interested in performing testing for outsourcing facilities could submit a drug master file (DMF) containing the information outlined below. Upon receipt of a letter from an outsourcing facility stating its intention to use the laboratory, FDA would review the DMF. If the review did not identify any questions regarding the content of the DMF, FDA would issue a letter to the DMF holder stating that FDA has no further comments. A copy of that letter would need to be provided to and be maintained by the outsourcing facility and produced during an inspection. Laboratory DMFs would need to contain the following:

- A description of the procedures for the conduct and documentation of each test to be conducted
- A description of how the methods and equipment for each test were found to be suitable for their intended use and capable of producing valid results
- A description of records to be maintained at the laboratory and/or provided to the outsourcing facility (e.g., out-of-specification (OOS) investigation)
- A description of the quality assurance activities performed, including:
  - qualification of lab analysts and their supervision
  - verification that analytical results reported to customers are accurate and complete
  - procedures for handling unexpected and out of specification results
  - maintenance of equipment used in testing, data analysis, and data storage
  - controls to ensure data integrity
- A commitment to update the DMF if the procedures described above are significantly modified
- A commitment to notify outsourcing facilities of specified changes or problems, such as investigations of its operations resulting from an OOS finding, a change in test method, or identification of an error in test results provided to the outsourcing facility

I. Stability/Expiration Dating

A stability program must be established to assess the stability characteristics of finished drug products, and the results of stability testing must be used to determine appropriate storage conditions and expiration dates (21 CFR 211.166). Stability testing is used to ensure that a drug product will retain its quality (for example, strength[16]) and remain sterile through the labeled expiration date. Procedures established for assessing the stability of drug products compounded by outsourcing facilities should achieve the following:

- Incorporate stability-indicating test methods that are reliable, meaningful and specific
- Evaluate samples of the drug product in the same immediate container closure system and with the same label that will be affixed to the container when the drug product is marketed
- Evaluate samples for stability that are representative of the lot or batch from which they were obtained and are stored under suitable conditions
- Incorporate testing to evaluate antimicrobial effectiveness (resistance to antimicrobial contamination) for drug products labeled or intended to be multiple dose
- Evaluate three (3) batches of each drug product to determine the expiration date

The Agency does not intend to take action against an outsourcing facility regarding stability studies if (1) a beyond-use date (BUD) has been established according to the bulleted criteria below, (2) the BUD provides reasonable assurance of chemical and physical stability based on literature or other scientific information, and (3) the BUD is used as the expiration date.[17]

- If the finished drug product is terminally sterilized and a sterility test has not been completed before release, the drug product is labeled with a BUD of not more than 14 days.

- If the finished drug product is aseptically processed and a sterility test has not been completed before release, the finished drug product is labeled with a BUD
  - not to exceed 24 hours at USP controlled room temperature;
  - not more than 3 days refrigerated;
  - not more than 45 days in a solid frozen state between -25° and -10°.

- If each batch of the finished drug product has a completed sterility test before release, the finished drug product is labeled with a BUD of not more than 14 days (at USP controlled room temperature or refrigerated) or not more than 45 days (in a solid frozen state between -25° and -10°) beyond completion of the sterility test (e.g., for a sterility test that takes 14 days to complete, the BUD would not exceed 28 days at USP controlled room temperature).

[16] For more information on strength and stability testing, see Allen Jr. L, Bassani G, Elder Jr. E, Parr A, for the USP Compounding Expert Committee. Strength and Stability Testing for Compounded Preparations.

[17] Under section 503B(a)(10)(A)(iii)(VI) of the FD&C Act, the compounded drug product must be labeled with an expiration date.

- Notwithstanding the conditions outlined above, for sterile preserved drugs, the finished drug product is labeled with a BUD of not more than 30 days beyond completion of the sterility test.

In addition, the Agency does not intend to take action against an outsourcing facility regarding stability testing if the drug product is composed solely of one or more drug products approved under section 505 of the FD&C Act, the approved drug product labeling specifies how to assign an *in-use time*, the compounded drug product has been compounded and labeled with an *in-use time* in accordance with the approved product labeling, and the in-use time is used as the expiration date. If two or more approved drug products are used in the compounded drug product, the in-use time for the compounded drug product should be the shortest of the in-use times specified by the drug product labeling.

If the drug product requires additional manipulation before administration or the labeling permits multiple entries of the container/closure system, appropriate studies should be conducted to support the labeled in-use time.

J. Packaging and Labels

Packaging of sterile drugs must be appropriate to the product and capable of ensuring the sterility and integrity of the product until it is administered to a patient (see §§ 211.94, 211.122). Labels must contain required information, and labeling operations must include controls to prevent mix-ups; furthermore, procedures must be developed to ensure these requirements are met (§§ 211.122, 211.125, 211.130, 211.134). The following aspects of packaging and labeling are critical to ensure the quality of compounded sterile drug products and are expected to be implemented by outsourcing facilities:

- The container, closure, and packaging systems provide adequate protection against foreseeable external factors in storage, shipment, and use that could cause contamination or deterioration of the finished drug product or any intermediate such as a stock solution (e.g., cracked vials, pinhole leaks in bags, frozen drug products).
- Adequate controls have been established for issuing labels, examining issued labels, and reconciliation of used labels to prevent mix-ups.
- There is physical/spatial separation between different labeling and packaging operations to prevent mix-ups.
- Adequate controls have been established to ensure proper identification of any filled containers of sterile drug products that will be stored unlabeled for any period of time.
- Packaging records include specimens of all labels used.
- The labeled finished drug product has been examined for accuracy and thoroughness before release.

K. Quality Assurance Activities/Complaint Handling

Quality assurance activities are needed to ensure that procedures are followed and a quality drug product is produced (§§ 211.22, 180, 192, 198). Part 211 requires that drug producers establish a quality control unit to oversee various aspects of sterile production.

It is expected that the quality control unit be independent; that is, the quality control unit should not take on the responsibilities of other units of the outsourcing facility's organization, such as the responsibilities handled by production personnel. In very limited circumstances, a single individual can perform both production and quality functions. That person is still accountable for implementing all the controls and reviewing the results of compounding operations to ensure that product quality standards have been met. Under such circumstances, it is recommended that another qualified individual, not involved in the production operation, conduct an additional, periodic review of quality control unit activities.

Procedures describing the role and responsibilities of the quality control unit must be established and followed (§ 211.22(d)). The following aspects of quality assurance and quality control are critical to ensuring the quality of compounded sterile drug products and are expected to be implemented by outsourcing facilities.

The quality control unit is responsible for discrepancy and failure investigations and the development and oversight of appropriate corrective actions and preventive actions regarding the following:

- Rejected lots of finished drug product, including initial positive sterility tests or out-of-specification results for attributes such as endotoxin level, assay, impurities, particulate matter, or reconstitution time, if applicable and regardless of batch disposition
- Unexpected results or trends
- Failures that occurred during validation or revalidation of sterilization or depyrogenation processes, including media fill/process simulation failures
- Stability failures, including failures of quality that are determined to have other causes than degradation of the drug product
- Environmental and personnel monitoring results that exceed alert or action limits
- Process deviations or equipment malfunctions that involve critical equipment, such as sterilizers and lyophilizers
- Returned goods that indicate possible drug product contamination or other risks to patients (e.g., hazy or cloudy drug product, foreign matter/particulates in injectable drug products, cracked or leaky containers)

The quality control unit has the responsibility to ensure that each batch of finished drug product is sampled and tested to ensure that it meets appropriate specifications for release (see §§ 211.22(a), 211.165(d)).

The quality control unit must periodically review records of compounding operations to evaluate the quality standards for each drug product to determine the need for changes in specifications or control procedures (§ 211.180(e)). As part of this review, the quality control unit should identify trends and evaluate quality indicators such as:

- For aseptic processing, all media fills/process simulations performed since the last review
- Results of environmental monitoring
- Results of personnel monitoring
- Results of water system testing, where water is used as a component in the drug product and is purified/processed on-site
- Results of finished drug product testing
- Periodic scrutiny of operations to ensure adherence to procedures and proper aseptic technique

The quality control unit is also responsible for evaluating written and oral complaints concerning the quality or purity of, or possible adverse reactions to, a drug product. Complaint handling procedures must include a determination as to the need for a full investigation and provisions for review to determine whether the complaint represents an adverse event that must be submitted to FDA (see §§ 211.198 and 310.305, and section 503B(b)(5) of the FD&C Act).

REFERENCES

The following references provide additional information regarding the recommendations outlined above.

ISO 14644-1 "Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness."

ISO 14644-6:2007 "Cleanrooms and Associated Controlled Environments – Part 6: Vocabulary."

FDA guidance for industry, *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*.[18]

FDA guidance for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements.*

FDA guidance for industry, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production.*

Allen Jr. L, Bassani G, Elder Jr. E, Parr A, for the USP Compounding Expert Committee. Strength and Stability Testing for Compounded Preparations. Available at http://www.usp.org/sites/default/files/usp_pdf/EN/2014-01-13__strength_versus_stability_testing_for_compounded_preparations_3.pdf.

[18] FDA guidance documents are available on the FDA webpage at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

GLOSSARY

Action Limit – An established microbial or airborne particle limit that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

Active Ingredient – Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Alert Limit – An established microbial or airborne particle limit giving early warning of potential drift from normal operating conditions and triggering appropriate scrutiny and follow-up to address the potential problem. Alert limits are always lower than action limits.

Aseptic – Free from germs that cause disease; sterile.

Aseptic Process– the process by which a sterile product is packaged in a sterile container in a manner that maintains sterility.

Aseptic Manufacturing Area – The classified part of a facility that includes the aseptic processing room and ancillary cleanrooms.

Batch – A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single compounding order during the same cycle of production.

Beyond Use Date (BUD) – A date beyond which a compounded drug product should not be used. A BUD is intended to notify the user of the period during which a compounded drug product's required quality characteristics (e.g., sterility, strength, purity, freedom from particulate matter) can be ensured.

Bioburden – The total number of microorganisms associated with a specific item prior to sterilization.

Biological Indicator (BI) – A population of microorganisms inoculated onto a suitable medium (e.g., solution, container or closure) and placed within appropriate sterilizer load locations to determine the sterilization cycle efficacy of a physical or chemical process. The challenge microorganism is selected based upon its resistance to the given process. Incoming lot D-value and microbiological count define the quality of the BI.

Cleanroom – A room designed, maintained, and controlled to prevent particle and microbiological contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness classification.

Component – Any ingredient intended for use in the manufacture of a drug product, including ingredients that may not appear in the final drug product.

Critical Area – An area designed to maintain sterility of sterile materials.

Critical Surface – Surfaces that may come into contact with or directly affect a sterilized product or its containers or closures.

Disinfection – A process by which surface bioburden is reduced to a safe level or eliminated.

Depyrogenation – A process used to destroy or remove pyrogens (e.g., endotoxin).

Endotoxin – A pyrogenic product (e.g., lipopolysaccharide) present in the bacterial cell wall. Endotoxins can lead to reactions in patients receiving injections ranging from fever to death.

Expiration date – A date on the drug product label that indicates how long the drug can meet applicable standards of identity, strength, quality, and purity under labeled storage conditions before it is used. Expiration dates are determined based upon product-specific studies evaluating the specific formulation of a drug product, the specific container in which it is to be stored, and the conditions to which it may be exposed. Temperature, humidity, and light are some of the factors that can affect whether and how much a drug product degrades over time.

HEPA Filter – A high-efficiency particulate air filter with minimum 0.3 μm particle retaining efficiency of 99.97 percent.

HVAC – Heating, ventilation, and air conditioning.

Intervention – An aseptic manipulation or activity that occurs in the critical area.

In-use time – The maximum amount of time that can be allowed to elapse between penetration of a container/closure system once the drug product has been sterilized, or after a lyophilized drug product has been reconstituted, and before patient administration.

Isolator – A decontaminated unit, supplied with Class 100 (ISO 5) or higher air quality that provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding cleanroom air and personnel).

Laminar Flow – An airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight line vector.

Operator – Any individual participating in the aseptic processing operation, including line set-up, filler, or maintenance, or any other personnel associated with aseptic line activities.

Pyrogen – A substance that induces a febrile reaction in a patient.

Unidirectional Flow – An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

915 ***Terminal Sterilization*** – The application of a lethal agent to sealed, finished drug products for
916 the purpose of achieving a predetermined sterility assurance level (SAL) of usually less than 10^{-6}
917 (i.e., a probability of a nonsterile unit of greater than one in a million).
918
919 ***Viable Particle*** – A particle that consists of, or supports, one or more live microorganisms.

Exhibit B

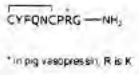
Declaration of Harold Patterson In Support Of QuVa's Motion To Set Required Bond Amount

Packaging and storage—Preserve at a temperature between 2° and 8°.

Expiration date—The expiration date is not later than 2 years after date of issue from manufacturer's cold storage.

Labeling—Label it to state that it is to be administered by intramuscular injection, in the recommended dose based on body weight.

Vasopressin



$C_{46}H_{65}N_{15}O_{12}S_2$ 1084.24

Vasopressin, 8-L-arginine [113-79-1].

DEFINITION

Vasopressin is a polypeptide hormone having the properties of causing the contraction of vascular and other smooth muscles, and of antidiuresis. It is prepared by chemical synthesis. It contains NLT 95.0% and NMT 105.0% of vasopressin ($C_{46}H_{65}N_{15}O_{12}S_2$), calculated on the anhydrous, acetic acid-free basis.

IDENTIFICATION

- **A.** The retention time of the vasopressin peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B. Mass Spectral Analysis**

Infusion solution: Acetonitrile, water, and trifluoroacetic acid (80: 20: 0.08)

Standard solution: 1 mg/mL of USP Vasopressin RS in water

Sample solution: 1 mg/mL of Vasopressin in water. [Note—The final concentrations of the *Standard solution* and the *Sample solution* can be adjusted, depending on the sensitivity of the mass spectrometer used in the testing.]

Instrumental conditions

(See *Mass Spectrometry* ⟨736⟩.)

Mode: LC/MS spectrometer

Interface/detection: Infusion system connected to an electrospray interface (positive ion)

Flow rate: 0.3 mL/min

Injection size: 10 µL

Analysis

Samples: *Standard solution* and *Sample solution*

Acceptance criteria: Should contain peaks with mass-to-charge ratios of 1084 and 543

ASSAY

- **Procedure**

Mobile phase: Dissolve 6.6 g of dibasic ammonium phosphate in 950 mL of water. Adjust with concentrated phosphoric acid to a pH of 3.0. Dilute with water to 1000 mL. To 870 mL of this solution add 130 mL of acetonitrile, and mix. Filter under vacuum through a nylon membrane of 0.45-µm pore size. [Note—The retention time of the vasopressin peak is very sensitive to small changes in acetonitrile concentration in the *Mobile phase*.]

System suitability solution: Dissolve suitable quantities of USP Lypressin RS and USP Vasopressin RS in 0.25% glacial acetic acid to obtain a solution having a known concentration of about 25 µg/mL of each substance.

Standard solution: Dissolve the entire contents of a vial of USP Vasopressin RS in a known volume of 0.25% glacial acetic acid. [Note—The solution may be diluted as necessary to a working concentration range for the *Assay*.]

Sample solution: Transfer about 10 mg of Vasopressin to a 25-mL volumetric flask. Dissolve in 0.25% glacial acetic acid, and dilute with the same solvent to volume.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; packing L1

Column temperature: 40 ± 1°

Flow rate: 1.0 mL/min

Injection size: 20 µL. [Note—The column is allowed to equilibrate for 1 h before making the first injection.]

System suitability

Samples: *System suitability solution* and *Standard solution*. [Note—Inject into an equilibrated liquid chromatograph, allowing about 60 min for complete elution.] [Note—The retention time of the vasopressin peak is between 6 and 9 min.]

Suitability requirements

Resolution: NLT 1.1 between the vasopressin and lypressin peaks

Relative standard deviation: NMT 2.0% for the vasopressin peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of vasopressin ($C_{46}H_{65}N_{15}O_{12}S_2$) in the portion of Vasopressin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Vasopressin RS in the *Standard solution* (mg/mL)

C_U = concentration of Vasopressin in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0% on the anhydrous, acetic acid-free basis

IMPURITIES

- **Ordinary Impurities:** The sum of the responses of impurities from the *Sample solution* in the *Assay* is NMT 5% of the area of the vasopressin peak.

SPECIFIC TESTS

- **Microbial Enumeration Tests** ⟨61⟩ and **Tests for Specified Microorganisms** ⟨62⟩: The total bacterial count is NMT 2×10^2 cfu/g. For products of animal origin, it also meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.
- **Water Determination,** *Method Ic* ⟨921⟩: NMT 8.0%
- **Acetic Acid in Peptides** ⟨503⟩: NMT 15.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, preferably of Type I glass, and store in a refrigerator.
- **USP Reference Standards** ⟨11⟩

USP Lypressin RS

USP Vasopressin RS

Vasopressin Injection

» Vasopressin Injection is a sterile solution of Vasopressin in a suitable diluent. Each mL of Vasopressin Injection possesses an activity of not less than 90.0 percent and not more than 110.0 percent of that stated on the label in USP Vasopressin Units. It may contain a suitable preservative.

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of Type I glass. Do not freeze.

Labeling—Label it to indicate its origin (animal or synthetic). Label it also to state the potency in USP Vasopressin Units per mL.

USP Reference standards ⟨11⟩—
USP Endotoxin RS
USP Vasopressin RS

Bacterial Endotoxins Test ⟨85⟩—It contains not more than 17.0 Endotoxin Units per USP Vasopressin Unit.

pH ⟨791⟩: between 2.5 and 4.5.

Particulate Matter in Injections ⟨788⟩—It meets the requirements under small-volume injections.

Other requirements—It meets the requirements under *Injections and Implanted Drug Products* ⟨1⟩.

Assay—

Mobile phase, System suitability solution, Chromatographic system, and *Procedure*—Proceed as directed in the *Assay* under *Vasopressin.*

Diluent—Dissolve 5.0 g of chlorobutanol in 5.0 mL of glacialacetic acid, add 5.0 g of alcohol, 1.1 g of sodium acetate, and 1000mL of water, and mix.

Standard preparation—Dissolve the entire contents of a vial ofUSP Vasopressin RS in a known volume of *Diluent.* [NOTE—The solution may be diluted as necessary to a workingconcentration range for the *Assay.*]

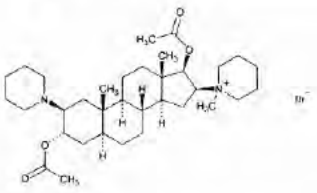
Assay preparation—Pipet 2.0 mL of Injection into a 25-mL volumetric flask, dilute with 0.25% glacial acetic acid to volume, and mix.

Procedure—Calculate the potency, in USP Vasopressin Units per mL, by the formula:

$$C(r_U / r_S)$$

in which C is the concentration, in USP Vasopressin Units per mL, of the *Standard preparation;* and r_U and r_S are the mean values of the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. [NOTE—The runtime should be long enough to allow for the elution of the chlorobutanol peak (approximately 60 minutes).]

Vecuronium Bromide



$C_{34}H_{57}BrN_2O_4$ 637.73

Piperidinium, 1-[(2β,3α,5α,16β,17β)-3,17-bis(acetyloxy)-2-(1-piperidinyl) androstan-16-yl]-1-methyl-, bromide; 1-(3α,17β-Dihydroxy-2β-piperidino-5α-androstan-16β,5α-yl)-1-methylpiperidinium bromide, diacetate [50700-72-6].

DEFINITION

Vecuronium Bromide contains NLT 98.0% and NMT 102.0% of $C_{34}H_{57}BrN_2O_4$, calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩: Meets the requirements
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution,* as obtained in the *Assay.*

ASSAY

- **PROCEDURE**

Diluent: Pipet 1.0 mL of 1 N hydrochloric acid into a 1000-mL volumetric flask, and dilute with acetonitrile to volume.

Solution A: Dissolve 8.0 g of sodium perchlorate in 6.0 mL of water, and dilute with acetonitrile to 1 L.

Solution B: Dissolve 1.6 g of ammonium chloride in 8 mL of ammonium hydroxide, and dilute with methanol to 1 L. [NOTE—Avoid excessive degassing to prevent the loss of ammonium hydroxide.]

Mobile phase: *Solution A* and *Solution B* (60:40)

Standard solution: 0.5 mg/mL of USP Vecuronium Bromide RS in *Diluent*

Sample solution: 0.5 mg/mL of Vecuronium Bromide in *Diluent*

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability.*)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 25-cm; 5-µm packing L3
Column temperature: 40°
Flow rate: 0.5 mL/min
Injection size: 20 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 5000 theoretical plates
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of vecuronium bromide ($C_{34}H_{57}BrN_2O_4$) in the portion of Vecuronium Bromide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Vecuronium Bromide RS in the *Standard solution* (mg/mL)
C_U = concentration of Vecuronium Bromide in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **ORGANIC IMPURITIES**

Cation suppressor regeneration solution: 0.02 M tetrabutylammonium hydroxide

Mobile phase
[NOTE—Filter components before combining. Avoid evaporation of tetrahydrofuran during degassing.]
Combine methanol, water, and hydrochloric acid (250:1500:1). Leave at room temperature for a few min. Add 45 mL of tetrahydrofuran, and then dilute with water to 2 L.
[NOTE—This applies to all of the solution preparations. The addition, with sonication, of a small amount of acetonitrile (NMT 0.5 mL per 25 mg) to the weighed quantity of the samples may be used to aid in dissolution. Shaking and sonication may also be used after the addition of the required amount of 2.5 mM hydrochloric acid.]

System suitability solution: 5 µg/mL each of
USP Vecuronium Bromide RS,
USP Pancuronium Bromide RS,
USP Vecuronium Bromide Related Compound A RS,
USP Vecuronium Bromide Related Compound B RS,

USP Monographs